SYNTHESIS OF BARBITURIC ACID DERIVATIVES

A THESIS

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by

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"For the Lord grants wisdom! His every word is a treasure of knowledge and understanding." (Proverbs 2:6). The author gratefully and humbly acknowledges his Creator and Redeemer who gave the talents to complete this course of study and research.

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SUMMARY

The purpose of this research was to develop a simple method for synthesis of 5-ethylbarbituric acid and 5-phenylbarbituric acid derivatives in which the hydrogen at the 5 position is replaced by an amine function. Due to reports of synergism of numerous drugs with barbiturates, it was considered that such compounds could have therapeutic value. The 5,5-dialkyl barbituric acids are a class of compounds known to possess pronounced hypnotic activity.

The 5-ethylbarbituric acid or 5-phenylbarbituric acid was prepared by condensing the appropriately substituted malonic ester with urea in dry absolute ethanol utilizing sodium ethoxide as the base. The 5-ethylbarbituric acid was then brominated with liquid bromine following dissolution of the barbiturate in hot water. The bromination of the 5-phenylbarbituric acid was accomplished in 0.6 N aqueous sodium hydroxide with bromine water. Replacement of the bromine atom with various amines was accomplished in methanol and the resultant uramil derivative could usually be isolated either following evaporation of the solvent or adjusting carefully the pH of the solution. Twenty-nine new barbituric acids have been prepared by this method.

Hydrolytic stabilities of barbiturates may often be correlated with their hypnotic properties. For this reason the stability of each of these compounds was determined in 95 per cent ethanol made 0.3 N in sodium hydroxide. It was found that each compound prepared was relatively stable to the base described on mixing and after being heated

in a constant temperature bath for two hours. Only changes in the extinction coefficients were observed. After the solutions had been allowed to stand for twenty-four hours the band at longer wavelength was observed to disappear on occasion when the amine of the barbiturate was secondary and occurred at the end of a chain. No simple correlation with steric hindrance based upon Newman "six numbers" was observed in the sampling of data taken.

The nuclear magnetic resonance spectra of these compounds reveal a usually broad singlet corresponding to the imide hydrogens between 8.00δ and 11.83δ. An interesting spectrum was observed for the 5-phenyl-5-[N-(2-aminopyrimidino)]-barbituric acid salt prepared. It is observed that on standing overnight in dimethylsulfoxide-d_6 two doublets appear where a single doublet is expected and two triplets appear where a single triplet is anticipated. Two additional singlets, each intergrating for less than one proton, also appear in the same region as the two doublets.

The mass spectrum of each new compound has been recorded and the fragmentation patterns peculiar to the types of compounds prepared are discussed along with the evidence they present for covalent bond formation between the amine and the barbituric acid moiety. Molecular ions were frequently observed; however, more often the amine function was lost in a McLafferty-type rearrangement or simply cleaved without concomitant hydrogen transfer to the carbonyl oxygen at either C_4 or C_6.

All of the new barbituric acid derivatives prepared in the course of this work are being submitted for physiological evaluation.

CHAPTER I

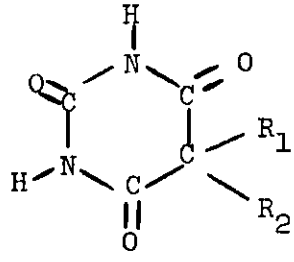
INTRODUCTION

During his famous studies on the constitution of uric acid, von Baeyer[6,7] isolated a previously unknown compound to which he gave the name "barbituric acid"[54] and showed that on cleavage it gave malonic acid and urea. Grimaux[48,49] first prepared barbituric acid from malonyl chloride and urea and established that it was a derivative of pyrimidine. Conrad and Guthzeit[20] prepared the first dialkyl derivatives, among them diethylbarbituric acid, many years before Fisher[34] discovered a convenient synthesis and, together with von Mehring described[33] its hypnotic properties. Barbital[52,19] (5,5-diethylbarbituric acid) was subsequently introduced into medicine under the name of "Veronal" and achieved such outstanding success that prolific research on derivatives of similar structures ensued. While the parent compound has no useful physiological activity, many of its derivatives have been found to have a pronounced depressant action on the central nervous system and are, therefore, valuable as sedatives, anesthetics, and soporifics.[26]

These cyclic diimides, which are usually prepared by condensing urea or thiourea with malonic esters, are commonly known as "barbiturates" where this term is used to designate a mono or polysubstituted barbituric acid or its salt. Although more than two thousand barbiturates have been prepared, only approximately twenty have achieved

appreciable therapeutic importance.[36] The barbiturates finding widest use as pharmaceuticals are the 5,5-disubstituted compounds, some of which are shown in Figure 1.[36]

Barbituric Acid



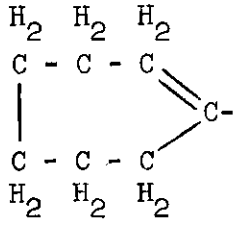
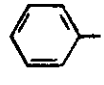
Drug	R_1	R_2	Action
Amobarbital	C_2H_5-	CH_3(-CH_3)-CH-CH_2-CH_2-	Intermediate
Barbital	C_2H_5-	C_2H_5-	Long
Butabarbital	C_2H_5-	CH_3-CH_2-CH(CH_3)-	Intermediate
Heptabarbital	C_2H_5-		Intermediate
Phenobarbital	C_2H_5 -		Long
Secobarbital	CH_2 = CH-CH_2-	CH_3-CH_2-CH_2-CH(CH_3)-	Short

Figure 1. Barbiturates

A related compound is Pentothal, sodium [the sodium salt of 5-ethyl-5-(1-methylbuty)-2-thiobarbituric acid], shown in Figure 2, which has been used clinically as an intravenous anesthetic.[68,69]

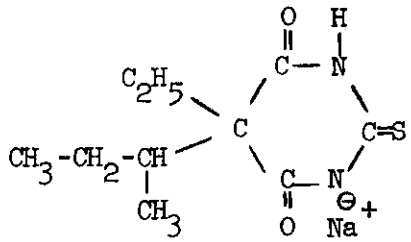


Figure 2. Pentothal, Sodium

While these commonly used barbiturates have a variety of uses and effects on living systems, it has been observed that these uses and effects can be enhanced by the administration of other materials either along with or prior to administration of the barbiturate. The term "synergism" has been applied to such actions and it may be defined as the combined action of two or more agents which is greater than the sum of the action of the agents used alone. Synergism is very commonly encountered in the field of medicine. It is not an uncommon practice to administer two or more therapeutic agents to a patient in order to accomplish that which these agents separately could not, or could with less efficiency.[25,11,13,45] Of considerable interest is the synergism observed between ethanol and barbiturates.[65] Graham reported[47] that the severity of symptoms of the ethanol and barbiturate combination was greater if the ethanol concerned had been taken as hard liquor rather

than in cases where a diluent had been employed. The explanation was proffered that the hard liquors irritated the gastric and duodenal mucosa and thus promoted the absorption of those drugs that were subsequently swallowed. Experimental evidence of the synergistic action between alcohol and phenobarbital was demonstrated by Jetter and McLean[53] by showing that death in rats could be produced regularly by a combination of nonfatal doses of each. The injection of thalidomide prior to barbiturate administration prolonged sleep in mice,[55] as did prior administration of LSD.[15] Colchicine was observed to reduce the induction time of barbital anesthesia[9] while acetylsalicylic acid administered thirty minutes before a subhypnotic dose of hexobarbital converted the latter to a hypnotic one in mice.[61] Respiratory arrest was found to occur in thirty per cent of a group of rats when morphine and hexobarbital were administered in subhypnotic doses.[62] A preparation of cannabis Americana, which did not produce perceptible hypnotic action in high doses when administered alone to mice, caused a marked increase in the hypnotic effect of butallylonal.[57] Conversion of a subhypnotic dose of hexobarbital to a hypnotic one by prior administration of sulfanilamide has also been observed[1] and possible synthetic routes to single molecules incorporating both of these type drugs have been investigated in this laboratory.[25]

It has been a considerable time now since a new effective sedative of the barbiturate series has been developed and D. G. Friend of the Harvard Medical School observed at a symposium sponsored by the Division of Medicinal Chemistry in 1963 that a need existed for chemists to reexamine the barbituric acid molecule.[37] It has been used as the

carrier for many synthetic active preparations, and might be utilized to make more effective use of other agents such as some of the antihistamine or tranquilizer preparations. He suggested the linking of the barbituric acid ring with other groups that have useful effects on the central nervous system and designated two specific molecules for possible preparation (Figure 3).[37] At this time, Doerr[25] had already begun synthetic studies to attempt linking the barbituric acid system to the sulfanilamide system.

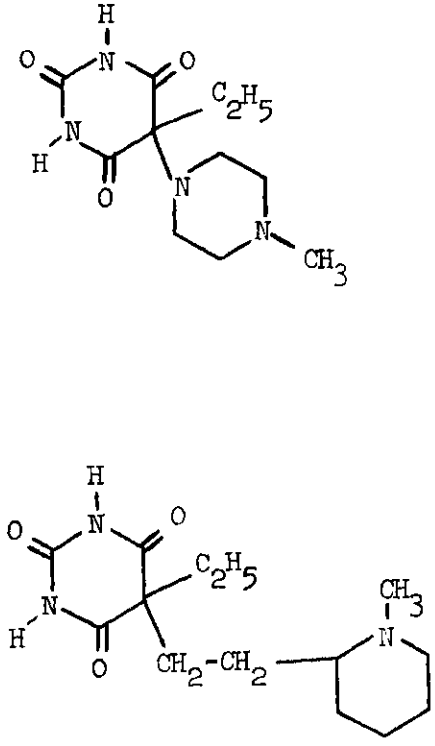


Figure 3. Suggested Compounds

This research has been concerned with the synthesis of novel barbituric acids, which could be considered derivations of 5-amino-barbituric acid commonly known as uramil (Figure 4). A primary or secondary amine with possible known physiological activity of its own could be introduced into the barbituric acid moiety at the five-

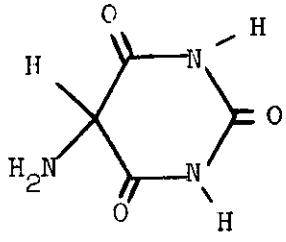


Figure 4. Uramil

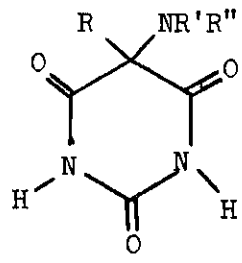
position of either a 5-phenyl or 5-ethylbarbituric acid. In alkaloids the presence of a cyclic nitrogen atom is stressed in the chemistry of these materials as the distinctive which sets them apart from other naturally occurring compounds.[23] For this reason a number of the amine functions of those molecules prepared contain one or more cyclic nitrogen atoms. Nearly all barbiturates of useful pharmacological activity, from the plethora of barbituric acid derivatives available, contain an ethyl group at the five-position.[27] The 5-phenyl derivatives were investigated since this is the simplest of the aromatic systems and to allow comparison with the aliphatic ethyl system. Barbital (5,5-diethylbarbituric acid) and phenobarbital (5-ethyl-5-phenylbarbituric acid) each demonstrate a relatively prolonged pharma-

cological action and are therefore classified as "long-acting" barbiturates. Phenobarbital is unique among members of the barbiturate series in showing a selective depressant action on the motor cortex and has for this reason long been used as a control for epilepsy.[27]

Even though each half of the molecule may possess a desirable physiological activity, one cannot a priori reach the conclusion that any of these compounds would possess unusual activity because of the activity of their component parts; however, a distinct possibility of such compounds exhibiting physiological activity does exist.

A few uramil derivatives are known and most of these are listed in Figure 5. In general, these were prepared by methods similar to that outlined by Gebauer in his patented process[41] and one of these, Eldoral, has found use as a sedative and hypnotic. This process involves nitrogen alkylation of a primary or secondary amine with a 5-halogen-5-alkyl-barbituric acid. A modification of this process has been attempted by Giudicelli, et al.[44] in which a malonic ester already containing the amine function (and an alkyl group) is condensed with urea.

The reaction sequence to be followed incorporates the general method utilized by Fischer and Dilthey[34] as a part of the reaction sequence to be followed for the synthesis of barbituric acid derivatives (Figure 6).



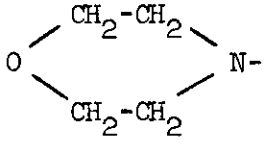
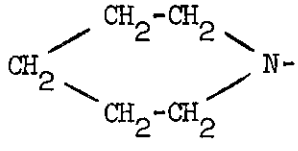
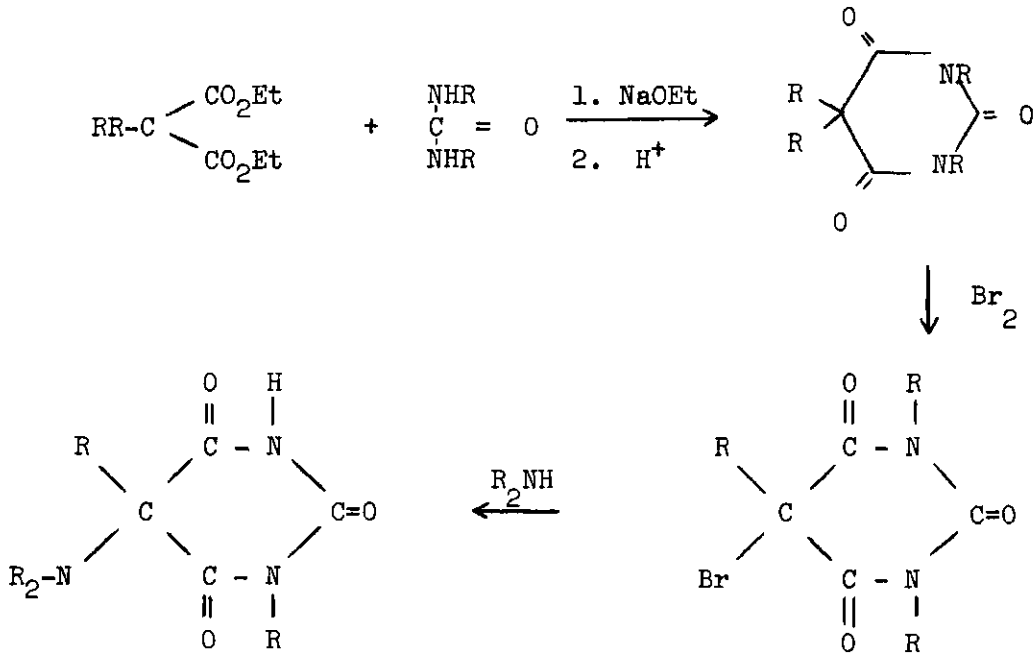
R'R"N-	R-	Reference
H_2N-	C_2H_5-	34
$(CH_3)_2N$-	C_2H_5-	43
$(CH_3)_2N$-	C_6H_5-	43
$(C_2H_5)_2N$-	C_2H_5-	38,16
$HO(CH_2)_2NH$-	C_2H_5-	38
C_6H_5NH-	C_2H_5-	18,42,17,41
C_6H_5-N(-C_2H_5)-	C_2H_5-	18
4-$C_2H_5OC_6H_4NH$-	C_2H_5-	18,42,17,41
	C_2H_5-	44
	C_2H_5-	41

Figure 5. Uramil Derivatives



R = H, aryl, alkyl

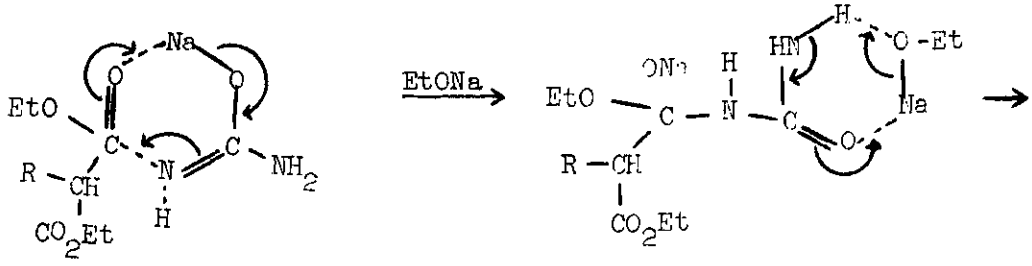
Figure 6. Reaction Sequence to be Studied

CHAPTER II

DISCUSSION OF EXPERIMENTAL RESULTS

Although Several preparations of barbituric acids are available in the literature[12,10] the most commonly used method is the condensation of malonic esters with urea, thiourea, guanidine, or their derivatives in an alcoholic media in the presence of alcoholates of alkali or alkaline earth metals.[10] In all cases the preparations used in this work were condensations of the appropriate ester with urea in absolute ethanol using soldium ethoxide as the base.

The mechanism of the condensation reaction has not been investigated in detail. However, Levina and Velichko in their review in Uspikhi Khimii[56] consider that the most plausible mechanism proceeds with the transfer of the reaction center, which they describe as a threefold "diene" synthesis with participation of σ, π -conjugated bonds.[56]



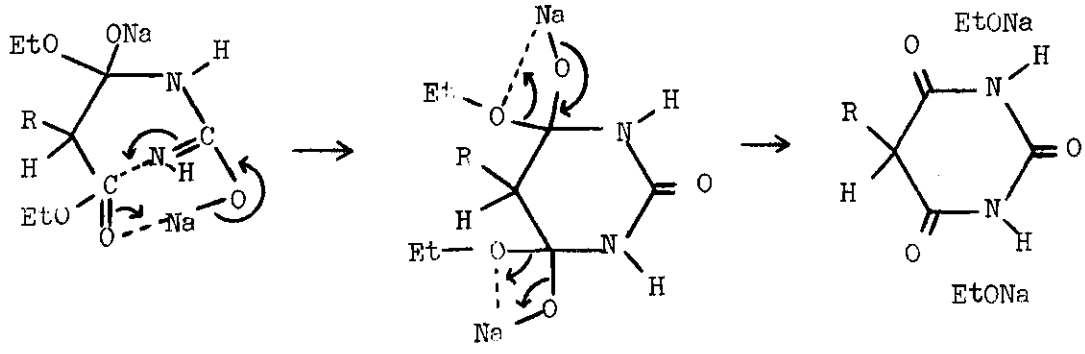


Figure 7. Mechanism of Levina and Velichko

The yields of the ethyl and phenylbarbituric acids from these condensation reactions were found over the course of several repetitions to be ca. 78 per cent and ca. 73 per cent, respectively. The bromination reactions took place in high yield as described in the literature[70,21] although side reactions were found to be problematic occasionally in the phenyl case in which a product melting over a wide range formed and from which the desired product could not be isolated. The mass spectrum of the bromine containing compounds was found to be most useful. The phenyl case showed the bromine doublet at the position calculated for molecular ions of the two isotopes of bromine (m/e 282,284). The ethyl case showed no peaks for molecular ions, but did show those corresponding to loss of ethyl (M-29) at 205 and 207.

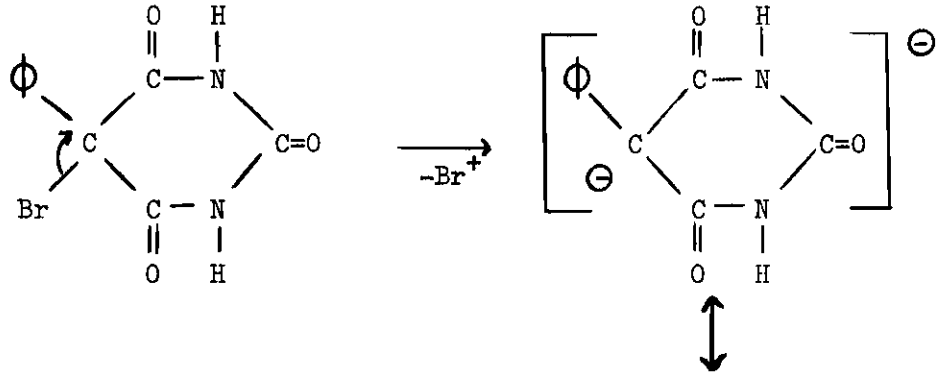
The method for preparations of the uramil derivatives was similar to those employed by Gebauer as described in the introduction[84] in his patented process for 5-methyl and 5-ethyl barbiturates with noteworthy modifications. The solvent in all cases was methanol. In

many cases, where one of the 5- positions was occupied by a phenyl group, precipitation was observed to occur on cooling the reaction mixture from the reflux temperature. However, more precipitation could be induced by removal of part or all of the solvent. When all of the solvent was removed from either the 5-phenyl or 5-ethyl derivative a resinous material almost always formed from which a crystalline substance could usually be separated on prolonged shaking with water. If this did not occur, the resin was dissolved in the minimal amount of acetone and water was added. Precipitation then occurred as the acetone was evaporated.

Any hydrobromide which was present with the free acid could be removed by washing with H_2O. Two exceptions should be noted. In the reaction between 5-bromo-5-phenylbarbituric acid and 2-amino-pyrimidine a salt separated from which the free barbituric acid derivative was not able to be washed free from the hydrobromide derivative. The same occurred in a similar reaction between the barbituric acid and 2,2,6,6-tetramethylpiperidine. These reactions both took place at room temperature. In each case, the micro-analyses confirmed the hydrobromide salt and no further attempt was made to obtain the free acid. It was found possible to separate the acid in good yield from the crude reaction product of 5-bromo-5-phenylbarbituric acid with p-phenetidine by dissolving in 0.6 N aqueous sodium hydroxide and extracting the residual amine with benzene. The free acid was then precipitated in good yield from the alkaline layer by addition of 10 per cent (w/w) sulfuric acid.

In several reactions the pH of the solution was found to be crucial. Cases in point were the two optical isomers of amphetamine which were separated by first making the acetone-water mixture acidic and then adjusting to a nearly neutral pH with ammonia. The desired product could thus be separated in near quantitative yield. It is quite possible that the yields could be improved in several cases by careful pH monitoring in the event any of the reactions being described should become synthetically important.

Some of the attempted preparations given in the experimental need special mention. In several cases a compound was isolated which analyzed for two more hydrogens than anticipated for the expected product. The spectral data obtained gave a reasonable fit for the formation of a salt. In at least one case, that of 5-phenyl-5[N-(anilino)]-barbituric acid, when the purification procedure included dissolving the product in 0.6 N aqueous sodium hydroxide, extracting with ether, and re-precipitating the acid with 10 per cent sulfuric acid a product was purified which analyzed for 5-phenylbarbituric acid. Possible mechanisms for the formation of these products are given in Figure 8.



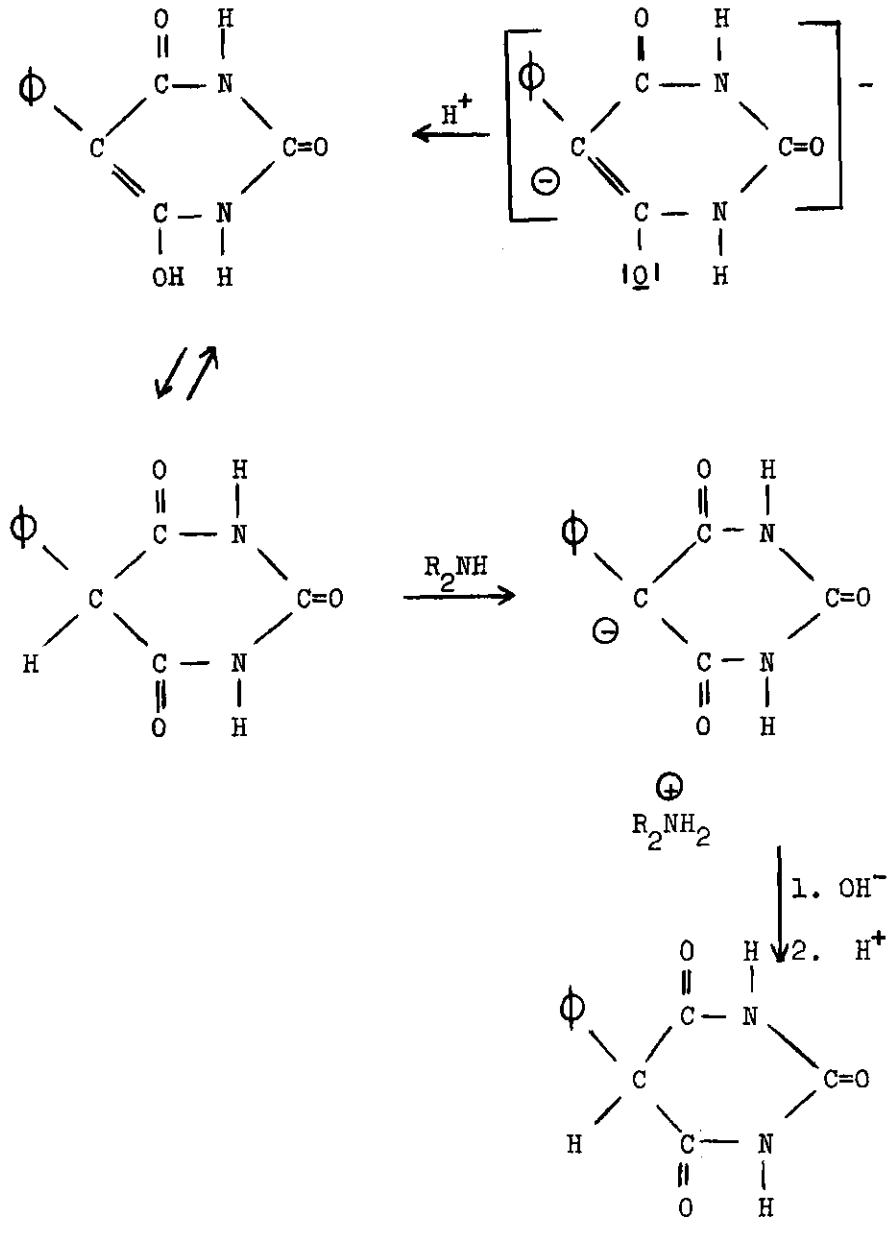


Figure 8. Possible Mechanisms for Formation of a Salt of 5-Phenylbarbituric Acid and/or 5-Phenylbarbituric Acid

Two alternate structures have been proposed for the compounds which have been prepared. The first of these is shown in Figure 9.

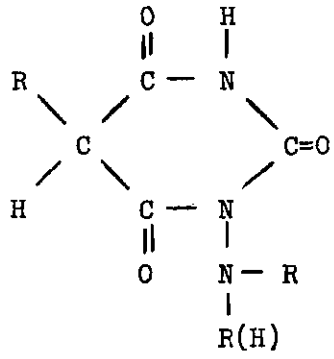


Figure 9. Hydrazine Type Structure.

A series of compounds of this structure have been prepared by Pohlmann and Busch[60a] by condensing the appropriately substituted semicarbazide with diethyl ethylmalonate. One compound which allows a comparison to the series being reported is the aniline derivative shown in Figure 10 which melts at 94-96°.

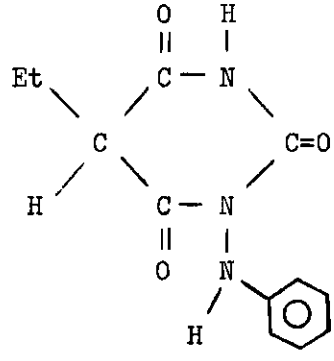


Figure 10. 5-Ethyl-1-[N-(anilino)]-barbituric Acid.

The corresponding 5-ethyl-5-[N-(anilino)]-barbituric acid which was first prepared by Gebauer[41] and then subsequently synthesized in this laboratory was found to melt at 240°. The unsplit singlet found at 11.03 δ integrating for two hydrogens also mitigates against a hydrazine type structure, since this signal is in the range of imide hydrogens of barbituric acids.

The second structure proposed could result from a Favorskii type rearrangement of the desired 5,5-disubstituted barbituric acid derivative although generally Favorskii rearrangements occur in the presence of strong bases rather than weak bases as was the condition in the above system. Such a structure would be similar to that shown in Figure 11.

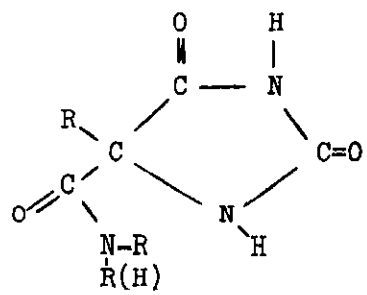


Figure 11. Product of Rearrangement.

The two equivalent imide hydrogens mentioned in the previous paragraph again suggest this is not the structure. A sharp amine hydrogen (on the nitrogen in position 5) is also discernible in a number of the spectra where the amine function is secondary. No amine hydrogen is present, obviously in the Favorskii type structure of Figure 11.

A titration of several of the new barbituric acid derivatives

was also attempted by dissolving the derivative in warm 95 per cent ethanol and titrating with aqueous HCl. Approximately one-half of an equivalent of HCl was required for the titration which may indicate that the compounds are zwitterionic in the solvent employed with the amine being protantated through an α-amino acid type structure as shown in Figure 12. According to these data the compounds titrated are slightly more basic than ethanol.

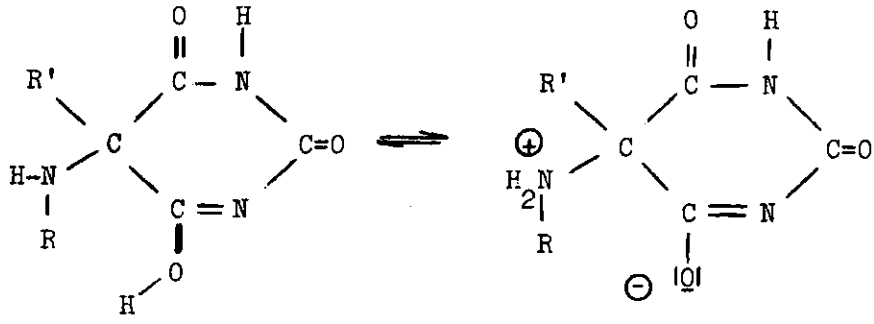


Figure 12. Possible Zwitterionic Form.

Some of the titration data and curves are recorded in Appendix D.

The spectral data which has been obtained along with the titration data strongly suggest that the compounds prepared are indeed, 5,5-disubstituted barbituric acids.

Elemental Microanalyses

Theoretically, it should be possible to form a salt between barbituric acids and amines rather than the type compounds being reported. Cogent evidence that this did not occur is given in the elemental microanalyses since a salt would analyze for two additional hydrogens. These analyses are consolidated from the experimental section into Tables 1 and 2.

Ultraviolet Spectra

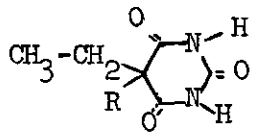
It has been shown[64] that a striking correlation exists between stability of the pyrimidine ring of the barbituric acid to hydrolysis and hypnotic activity. This stability has been formulated into a number of rules.

Following Doran,[27] these rules relating molecular structure to hypnotic potency may be stated as follows:

1. For a barbiturate to be hypnotically active, both of the hydrogen atoms in the 5-position must be replaced by substituents -- usually alkyl groups.
2. Increasing the length of primary 5-alkyl chains increases the hypnotic potency.
3. Chain branching in primary 5-alkyl substituents increase the hopnotic potency. Branching is even more effective if it occurs in the alpha-carbon atom, so that the alkyl group is secondary rather than primary.
4. Barbiturates with a 5-alicyclic substituent are more active than the corresponding compounds in which the alicyclic group has been

Table 1

Derivatives of 5-Ethylbarbituric Acid



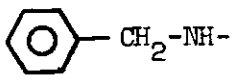
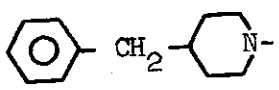
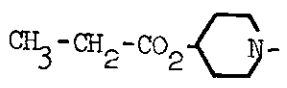
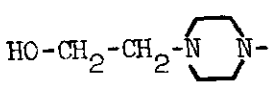
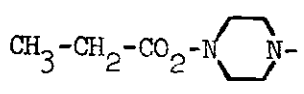
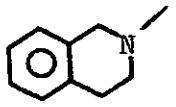
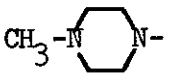
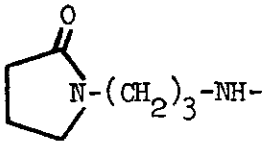
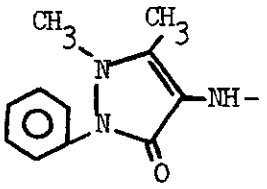
R	M.P. °C	% Yield	Percentage Calculated C	H	N	Percentage Found C	H	N
	217-218°	61	59.76	5.79	16.08	59.62	5.78	15.98
	239-240°	82	49.79	6.27	17.42	49.81	6.28	17.33
	215-216°	73	65.63	7.04	12.76	65.70	7.13	12.79
	189-190°	31*	54.01	6.80	13.50	53.97	6.88	13.47
	264-265°	38	50.69	7.09	19.71	50.83	7.12	19.64
	160-161°	32	49.99	6.45	17.94	50.03	6.56	17.79

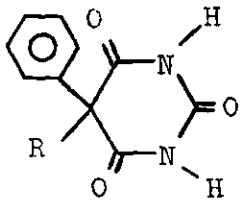
Table 1 Con't

R	M.P. °C	% Yield	Percentage Calculated C	H	N	Percentage Found C	H	N
	281 - 282°	39	62.71	5.96	14.62	62.66	6.02	14.53
	283 - 284°	31	51.96	7.13	22.03	51.79	7.22	21.92
	251 - 252°	25	52.69	6.80	18.91	52.81	6.88	18.80
	233 - 234°	36	57.14	5.36	19.60	57.26	5.53	19.50

*Product is somewhat soluble in solvent used for recrystallization.

Table 2

Derivatives of 5-Phenylbarbituric Acid



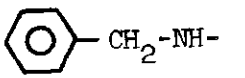
R	M.P. °C	% Yield	Percentage Calculated C	H	N	Percentage Found C	H	N
CH_3-CH_2-CH_2-NH-	180-181°	92	59.76	5.79	16.08	59.86	5.79	15.79
	203-204°	85	66.01	4.89	13.58	66.18	4.99	13.45
CH_3-O-$(CH_2)_2$-NH-	76-78°	94	56.31	5.45	15.15	56.09	5.72	14.99
CH_2=CH-CH_2-NH-	185-186°	83	60.23	5.05	16.21	60.09	5.10	16.31
HO-$(CH_2)_3$-NH-	190-191°	88	56.31	5.45	15.15	56.39	5.51	15.05

Table 2 Con't

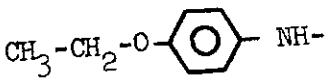
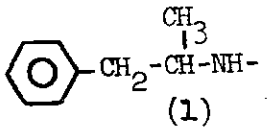
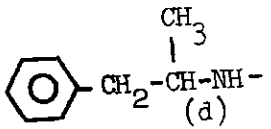
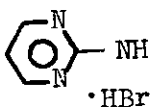
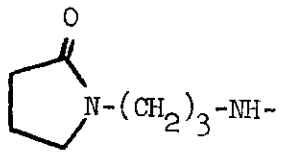
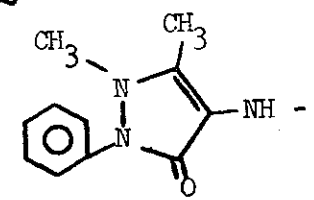
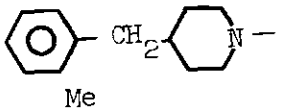
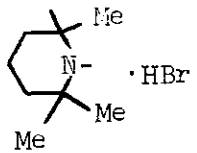
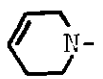
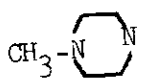
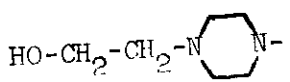
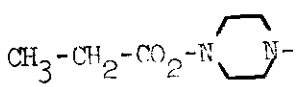
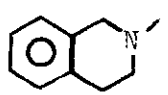
R	M.P. °C	% Yield	Percentage Calculated C	H	N	Percentage Found C	H	N
	246-247°	61	63.71	5.05	12.38	63.89	5.09	12.26
 (l)	181-182°	93	67.64	5.68	12.45	67.65	5.70	12.39
 (d)	181-182°	93	67.64	5.68	12.45	67.50	5.77	12.46
	169-170°	81	44.46	3.20	18.52	44.73	3.22	18.38
			Br = 21.02%			Br = 21.02%		
	237-238°	84	59.29	5.85	16.27	59.22	5.92	16.13
	228-229°	62	62.22	4.72	17.27	62.14	4.87	17.14

Table 2 Con't.

R	M.P. °C	% Yield	Percentage Calculated C	H	N	Percentage Found C	H	N
	263-264°	90	58.13	5.23	14.52	58.26	5.41	14.4
	243-244°	86	70.00	6.14	11.13	70.01	6.18	11.08
	251-252°	72	53.78	6.18	9.90	53.99	6.23	10.0
			Br - 18.83%			Br - 18.73%		
	192-193°	83	63.15	5.30	14.73	63.07	5.33	14.5
	245-246°	71	59.59	6.00	18.53	59.37	6.04	18.4
	246-246.5°	67	57.82	6.06	16.86	57.59	6.18	17.0
	211-212°	90	56.70	5.55	15.55	56.49	5.57	15.3
	236-237°	54	68.05	5.11	12.53	68.13	5.18	12.41

replaced by a straight-chain radical containing the same number of carbon atoms.

5. Replacement of an imide hydrogen on the pyrimidine ring by an alkyl group enhances the hypnotic potency.

6. Introduction of halogen (commonly a bromo group) into a 5-alkyl substituent enhances the hypnotic potency.

7. Introduction of an ethylenic linkage into a 5-alkyl substituent enhances the hypnotic potency.

8. Complete loss of hypnotic properties occurs when polar and semi-polar groups such as hydroxyl, amino, alkylamino, carbonyl, carboxyl, and sulfonyl are present in substituent groups.

Each of these rules may be explained on the basis of hydrolytic stability.[64] For this reason a qualitative study of the stability of new compounds produced was attempted as a portion of the present study.

Barbiturates are attacked by hydroxyl ion with concomitant destruction of the ring system.[40,35,39,3,4] Several plausible mechanisms have been given and these are summarized by Garrett[40] and are shown in Figure 13.

Eriksson and Holmgren investigated[31] the rates of hydrolysis of numerous 1-methyl-5,5-disubstituted barbiturates and were not able to establish a definitive linear free energy relation. They assigned substituent effects on reactivity to steric causes. All compounds with a 5-methyl group were found to be rapidly hydrolyzed while branching plus high molecular weight alkyl groups in the 5-position gave

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co-workers published[40] a kinetic study of the hydrolysis of twelve different 5,5-disubstituted barbituric acids in 1971. They followed the alkaline hydrolyses of these compounds spectrophotometrically and found rate-pH profiles of all compounds studied to be similar. All profiles were explained by hydroxyl-ion attack on the undissociated and monoanion forms of the barbiturate.[50] They also used Eriksson's detailed data[31,32] of second-order rate constants for the alkaline hydrolysis of 1-methyl-5,5-disubstituted barbituric acids and correlated these with total Newman "six numbers".[46] This rule states that those atoms which are most effective in providing steric hindrance to addition are separated from the attacking atom in the transition state by a chain of four atoms which means that if either the attacking atom or the carbonyl oxygen is designated "1", the "blocking atom" will be in the "6" position.[46] A linear plot was obtained in all cases. However, the slope of the curve where one of the substituents at the 5-position was methyl was different than the curves for substituents other than methyl. This was thought to indicate that the rate of hydrolyses may not be a function of steric effects alone. It should be noted that the only two compounds which fall markedly off their respective lines are the cyclohexenyl and bromoallyl derivatives. The work presently being reported could afford a new series of compounds for an excellent study of the effect of electronegative groups in the 5-position.

Since most barbituric acids* are found in the urine only in

*The long-acting barbiturates, such as barbital and phenobarbital, are found present in considerable amounts in the urine after ingestion.[27]

traces, it has been suggested[27] that the metabolic inactivation of these drugs involves a splitting of the barbiturate ring with formation of acetylurea and acetamide derivatives.

It has been shown[23,67,30] that 5,5-disubstituted barbituric acids invariably have no ultraviolet spectra in neutral media with the notable exception of the 1'-alkyl spiro-amino barbituric acids. This exception has been explained by Daugherty[23] by assuming the presence of zwitterionic species.

Stuckey has shown[66] from a spectral study of barbital and phenobarbital and their 1-methyl and 1,3-dimethyl derivatives in alkaline media that amido-imidol tautomerism involving only the hydrogen in the one-position occurs producing a two-hydroxy compound with an olefinic linkage. This is shown in Figure 14.

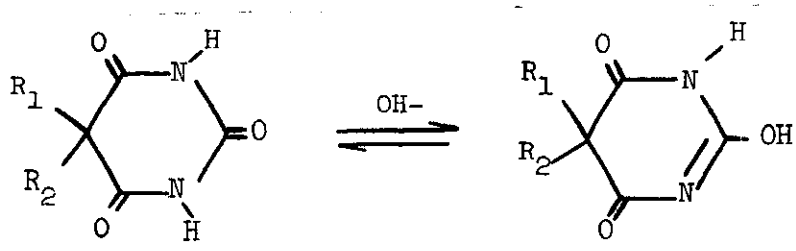


Figure 14. Amido-imidol Tautomerism

In the present work an attempt has been made to determine the stability of the various barbiturates prepared in 95 per cent ethanol which has been made 0.3 N in sodium hydroxide. Concentration of the substrate for these hydrolyses reactions ranged from 10^{-4} M to 10^{-5} M.

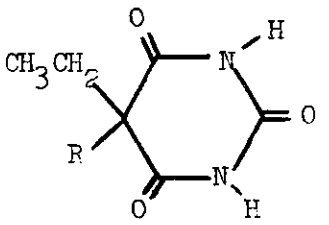
The ultraviolet region was scanned from 350 nm. to the end absorption which usually occurred ca. 225 nm. The studies were done with the aid of a Cary Model 14 Recording Spectrophotometer. The initial scan was obtained as soon as possible after dissolution of the sample and the same region was again scanned after heating for two hours in a constant temperature bath maintained at 60° ± 5°. The spectral data obtained are reproduced in Tables 3 and 4.

The λ_{max} for the uramil derivatives prepared may be seen to fall within a rather narrow range from 259 nm to 269 nm (with the exception of the pyrimidine derivative which was obtained as a hydrobromide salt) unless the five substituent itself absorbed in the ultraviolet region. This band was not found to shift significantly after the aforementioned heating or after subsequently standing 24 hours. No simple correlation appears to exist between total Newman "six number" and stability in the cases studied. It further does not appear that a simple generalization may be made comparing the hydrolyses of phenylbarbituric acids and ethylbarbituric acids containing the same amine function. However, it does seem that in cases where the amine function is part of a straight chain the hydrolysis is more rapid than in cases where the amine is part of a cyclic system. In all cases the barbituric acids prepared were found to exhibit the same spectra (with change in extinction coefficient) following the two hour heating period. Sometimes the band in the 259 nm-269 nm region would have disappeared after twenty-four hours had elapsed following heating.

Table 3

Wavelengths and Extinction Coefficients

of Derivatives of 5-Ethylbarbituric Acid*



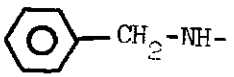
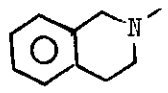
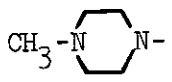
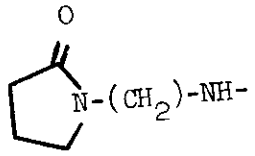
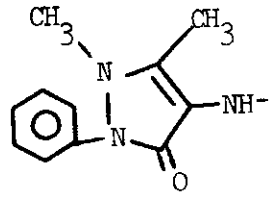
R	On Mixing	After Heating 2 hrs. at 60°C	After Subsequently Standing 24 hrs.
	λ nm max	λ nm max	λ nm max
H	(229)[a] 5,760 269 12,500		
	(226)[a] 13,900 260 6,340	(226)[a] 13,800 260 5,000	(226)[a] 9,400 260 2,200

Table 3 Con't

	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
	(226)[a]	17,200	(226)[a]	17,600	(226)[a]	18,500
	263	9,180	263	9,020	263	8,600
	(226)[a]	18,600	(226)[a]	22,000	(226)[a]	21,200
	262	11,300	262	10,200	262	10,700
	(226)[a]	15,900	(226)[a]	12,800	(226)[a]	8,820
	259	7,560	259	6,020	259	2,440
	(226)[a]	24,000	(226)[a]	13,300	(226)[a]	12,300
	256	14,400	256	11,000	256	10,900

[a]End absorption.

*Observed in 0.3 N NaOH in 95% EtOH.

Table 3 Con't

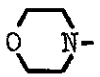
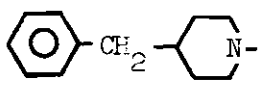
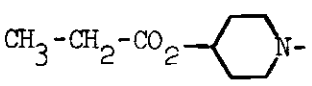
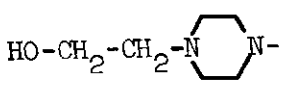
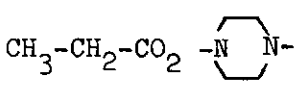
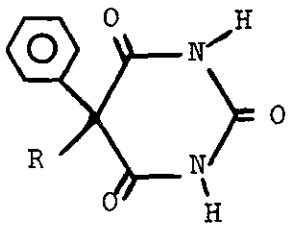
	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
	(226)[a] 262	17,300 11,400	(226)[a] 262	18,200 11,000	(226)[a] 262	19,000 10,900
	(226)[a] 261	14,800 7,060	(226)[a] 261	14,700 7,300	(226)[a] 261	14,600 7,400
	(226)[a] 262	16,400 9,960	(226)[a] 262	17,800 9,800	(226)[a] 262	19,200 9,800
	(225)[a] 262	15,400 7,080	(226)[a] 262	14,800 7,020	(226)[a] 262	15,000 7,220
	(225)[a] 262	15,700 7,340	(225)[a] 262	14,800 7,120	(225)[a] 262	15,400 7,420

Table 4

Wavelengths and Extinction Coefficients

of Derivatives of 5-Phenylbarbituric Acids*



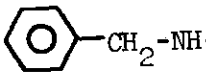
R	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
H	(226)[a]	7,800				
	271	17,000				
$CH_3-CH_2-CH_2-NH-$	(226)[a]	18,000	(226)[a]	13,200	(225)[a]	2,030
	261	6,520	261	4,880		
	(226)[a]	24,800	(226)[a]	14,200	(226)[a]	4,180
	261	7,790	261	4,420		

Table 4 Con't

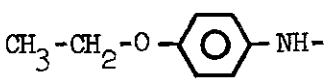
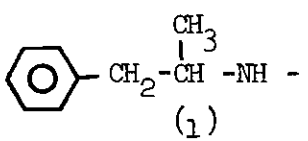
R	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
CH_3-O-(CH_2)-NH-	(226)[a]	21,600	(226)[a]	21,600	(226)[a]	8,330
	262	7,580	262	4,270	263	910
CH_2=CH-CH_2-NH-	(226)[a]	16,700	(226)[a]	10,500	(226)[a]	9,450
	263	5,520	263	2,880		
HO-(CH_2)$_3$-NH-	(226)[a]	14,300	(226)[a]	13,300	(225)[a]	2,940
	262	4,880	262	5,760		
	(226)[a]	27,800	(225)[a]	24,800	(226)[a]	19,000
	247	20,000	247	17,900	245	16,200
	268(sh)	9,090	268(sh)	7,330	310	2,640
 (1)	(226)[a]	27,900	(226)[a]	15,900	(226)[a]	9,030
	260	9,850	260	4,510		

Table 4 Con't

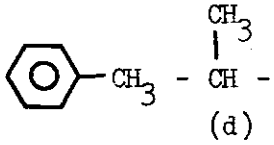
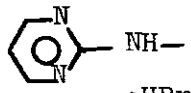
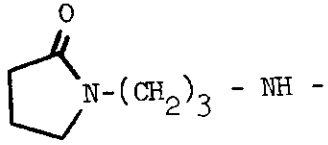
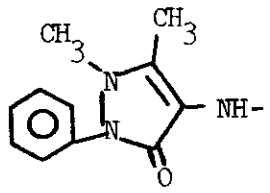
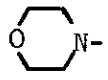
R	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
	(226)[a] 260	27,100 9,940	(226)[a] 260	15,600 4,270	(226)[a]	8,480
	(227)[a] 278	27,200 6,700	(227)[a] 273	24,100 5,820	(227)[a] 272	24,400 22,300
	(226)[a] 259	15,900 7,560	(226)[a] 259	12,800 6,020	(226)[a] 259	8,820 2,440
	(226)[a] 256	22,600 12,800	(226)[a] 256	8,420 8,420	(226)[a] 256	11,200 8,790
	(225)[a] 265	20,900 6,360	(225)[a] 265	21,300 9,390	(225)[a] 265	15,200 4,600

Table 4 Con't

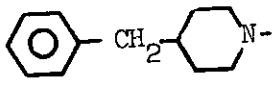
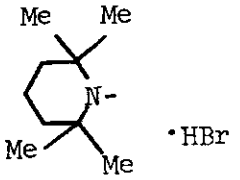
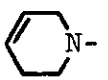
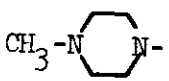
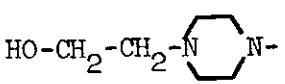
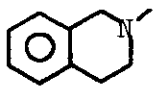
R	On Mixing λ_{max} nm		After Heating 2 hrs. at 60°C λ_{max} nm		After Subsequently Standing 24 hrs. λ_{max} nm	
	(226)[a] 264	22,500 6,730	(226)[a] 264	21,200 9,090	(226)[a] 264	22,700 9,580
	(227)[a] 269	13,700 7,030	(227)[a] 269	9,730 9,730	(227)[a] 269	11,800 10,200
	(226)[a] 264	23,900 7,610	(226)[a] 264	22,800 7,520	(226)[a] 264	24,900 8,000
	(226)[a] 265	15,200 5,180	(226)[a] 265	20,100 7,610	(226)[a] 266	10,700 3,730
	(226)[a] 264	21,900 6,450	(226)[a] 264	17,900 6,270	(226)[a] 264	19,700 6,700

Table 4 Con't

R	On Mixing		After Heating 2 hrs. at 60°C		After Subsequently Standing 24 hrs.	
	λ_{max} nm		λ_{max} nm		λ_{max} nm	
$CH_3-CH_2-CO_2-N$ (1,3-diazole)	(225)[a]	15,700	(225)[a]	14,800	(225)[a]	15,400
	262	7,340	262	7,120	262	7,420
	(225)[a]	27,100	(226)[a]	24,800	(226)[a]	28,200
	265	8,030	265	6,540	265	8,880

*Observed in 0.3 N NaOH in 95% EtOH

[a] End absorption

Each of the uramil derivatives prepared exhibited end absorption in the narrow range of 225 nm to 227 nm both before and after heating and also after standing twenty-four hours.

Infrared Spectra

The infrared spectra of the barbituric acids and starting compounds were recorded using a Perkin-Elmer Model 700 double-beam recording spectrophotometer. Records were obtained in the spectra of solid compounds from compressed potassium bromide discs (0.1 g) containing approximately one per cent of the compound being analyzed. Examination of the spectra of liquids was made using liquid films without a solvent. The infrared spectra of all new compounds are in Appendix A.

It does not seem possible to recognize barbituric acids as a class of organic compounds via the occurrence of any characteristic absorption bands in their infrared spectra.[22] However, it does appear that one may often state that the desired adduct is not present or is severely contaminated if a band appears ca. 1590 cm^{-1}. This band may be attributed to amine salts.[29]

In general the infrared curves revealed a carbonyl absorption between 1690 cm^{-1} and 1760 cm^{-1} which appeared either as a single broad peak or a doublet. With the exception of bands characteristic of the substituent introduced into the barbituric acid moiety, no further band assignments were made.

Nuclear Magnetic Resonance Spectra

Most of the published work on the application of nuclear

magnetic resonance spectroscopy to the identification of barbiturates has been done by Avdovich and Neville[5] and Neville and Cook.[60] Ruecher has also suggested[63] a method for determining barbiturates in a mixture in concentrations not sufficient for usual NMR analyses by use of a time averaging computer technique.

Nuclear magnetic resonance spectra in the present study were obtained using a Varian A-60A PMR spectrometer at ambient probe temperature of 40 ± 2°C. Tetramethylsilane (TMS) was used as an internal reference. Spectra were usually obtained in dimethyl sulfoxide-d_6 (although some spectral data in trifluoroacetic acid or acetone d_6 are reported in the experimental). All spectra reported in Tables 5 and 6 were recorded in dimethyl sulfoxide-d_6. The concentration of the barbiturates was approximately 10 per cent in solute by weight in order to observe the salient spectral features through a noisy baseline.

Neville and Cook observed[60] that the shifts due to solvent effects were in the order for trifluoroacetic acid > deuterochloroform > dioxane > dimethyl sulfoxide. These were also observed in the spectra of the new compounds reported in Tables 3 and 4 for the two solvents used. They depict these solute-solvent interactions as shown in Figure 15.[60]

The NMR spectra of nearly all compounds studied in this series showed a single, sometimes broad, absorption between 8.0 δ and 11.8 δ which has been attributed to the imide NH protons. This, however, does not preclude the possibility of tautomerism (Figure 16) because the concentration of one of the tautomers in equilibrium in the solvents

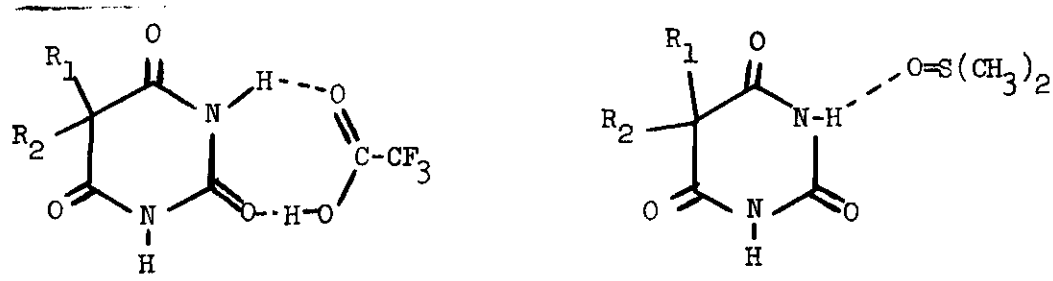


Figure 15. Solvent Effects

employed could be too small to be detected.

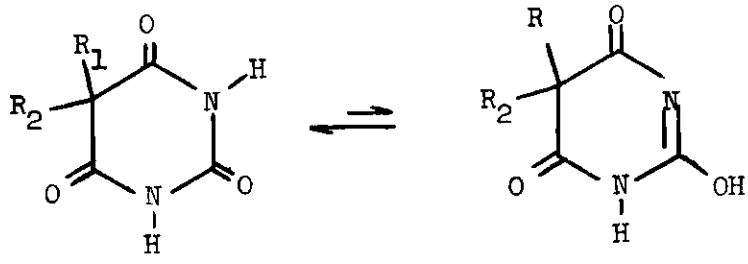


Figure 16. Tautomerism

The quartet, attributable to the methylene protons of the 5-ethyl group being split by methyl, were found within the narrow range of 1.77 δ to 1.96 δ. The only exception found was for the case of 5-bromo-5-ethylbarbituric acid. The triplet of the methyl group was found to lie between 7.30 δ and 7.53 δ in all cases. The shift and integral parameters of all three of these values are in good agreement with those reported for other barbituric acids.[5,60]

Table 5

NMR Shift Values in Units of δ for

Derivatives of 5-Ethylbarbituric Acid

as Observed in DMSO-d_6*

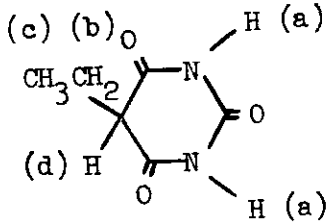
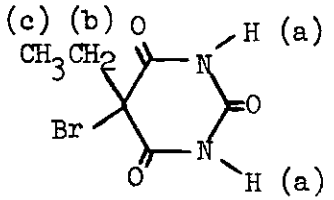
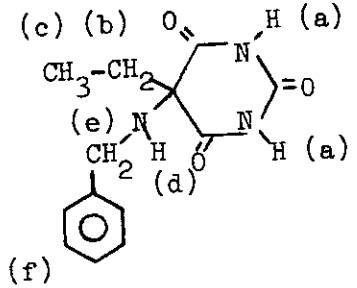
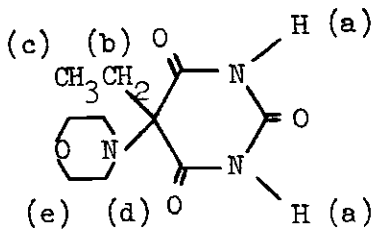
	(a)	(b)	(c)	(d)
	11.23 (singlet, 2H)	1.90 (multiplet, 2H)	0.83 (triplet, 3H)	3.53 (singlet, 1H)
	(e)	(f)	(g)	(h)
	-	-	-	-
	(a)	(b)	(c)	(d)
	11.82 (singlet, 2H)	2.33 (quartet, 2H)	0.83 (triplet, 3H)	-
	(e)	(f)	(g)	(h)
	-	-	-	-

Table 5 Con't



(a)	(b)	(c)	(d)
11.52 (singlet, 2H)	1.78 (quartet, 2H)	0.73 (triplet, 3H)	2,45 (singlet, 1H)

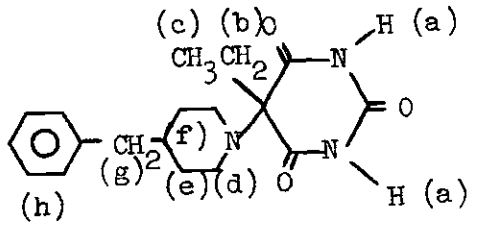
(e)	(f)	(g)	(h)
3.45 (singlet, 2H)	7.23 (singlet, 5H)	-	-



(a)	(b)	(c)	(d)
11.37 (singlet, 2H)	1.80 (quartet, 2H)	0.60 (triplet, 3H)	2.42 (singlet, 4H)

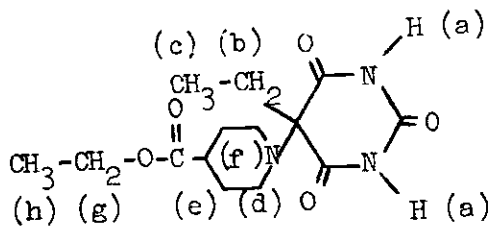
(d)	(e)	(f)	(g)
3.42 (singlet, 4H)	-	-	-

Table 5 Con't



(a)	(b)	(c)	(d)
11.33	1.78	0.63	2.72(eq)
(doublet, 2H)	(quartet, 2H)	(triplet, 3H)	(multiplet, 4H)

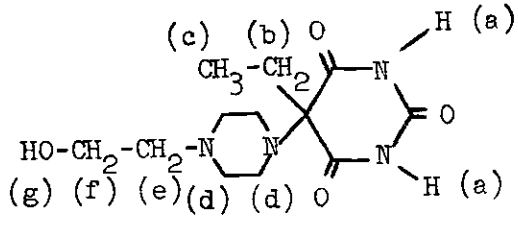
(e)	(f)	(g)	(h)
2.13 (ax)	1.30	2.37	7.06
(multiplet, 4H)	(multiplet, 1H)	(doublet, 2H)	(singlet, 5H)



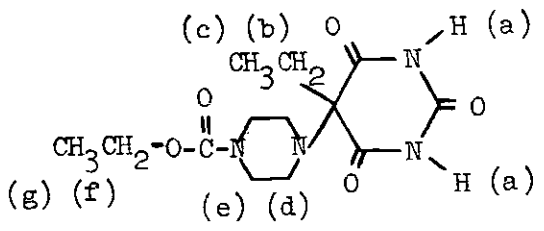
(a)	(b)	(c)	(d)
11.50	1.80	0.72	2.50
(singlet, 2H)	(quartet, 2H)	(triplet, 3H)	(multiplet, 4H)

(e)	(f)	(g)	(h)
1.73	1.73	4.03	1.15
(multiplet, 5H)	(multiplet, 5H)	(quartet, 2H)	(triplet, 3H)

Table 5 Con't.



(a)	(b)	(c)	(d)
11.33 (singlet, 2H)	1.95 (quartet, 2H)	0.72 (triplet, 3H)	2.42 (multiplet, 8H)
(e)	(f)	(g)	(h)
2.33 (triplet, 2H)	3.50 (triplet, 2H)	-	-



(a)	(b)	(c)	(d)
11.57 (singlet, 2H)	1.88 (quartet, 2H)	0.77 (triplet, 3H)	2.85 (singlet, 4H)
(e)	(f)	(g)	(h)
3.32 (singlet, 4H)	4.03 (quartet, 2H)	1.13 (triplet, 3H)	-

Table 5, Con't.

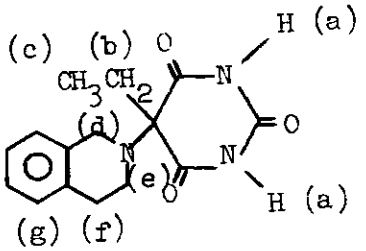
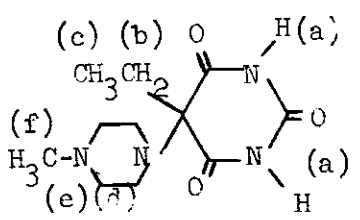
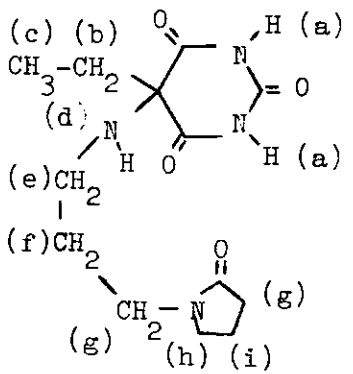
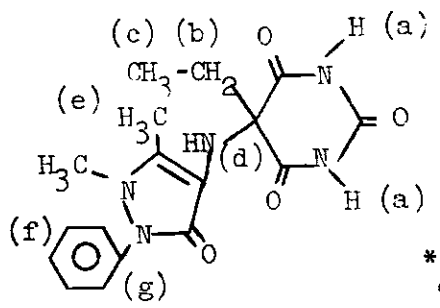
(h)		(a)	(b)	(c)	(d)
		9.08 (singlet, 2H)	1.77 (quartet, 2H)	0.68 (triplet, 3H)	4.12 3.70 (2 singlets, 2H)
		(e)	(f)	(g)	(h)
		2.80 (multiplet, 2H)	3.23 (multiplet, 2H)	6.81 (singlet, 2H)	6.92 (singlet, 2H)
		(a)	(b)	(c)	(d)
		-	1.77 (quartet, 2H)	0.60 (triplet, 3H)	2.38 (singlet, 4H)
		(e)	(f)	(g)	(h)
		2.20 (singlet, 4H)	1.90 (singlet, 3H)	-	-

Table 5 Con't



(a)	(b)	(c)	(d)
11.48 (singlet, 2H)	1.70 (quartet, 2H)	0.65 (triplet, 3H)	
(e)	(f)	(g)	(h)
2.40 (triplet, 2H)	1.42 (multiplet, 2H)	3.07 or 3.17 (triplet, 2H)	2.05 (triplet, 2H)
		(i) ~1.85 (multiplet, 2H)	(j) 3.07 or 3.17 (triplet, 2H)



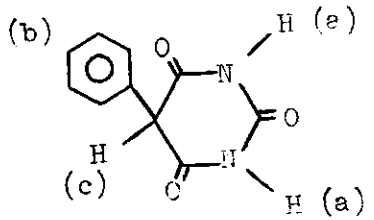
(a)	(b)	(c)	(d)
10.85 (singlet, 2H)	1.83 (quartet, 2H)	0.92 (triplet, 3H)	4.87 (singlet, 1H)
(e)	(f)	(g)	(h)
2.73 (singlet, 3H)	2.11 (singlet, 3H)	7.35 (singlet, 5H)	-

* TMS was employed as an internal reference in all cases.

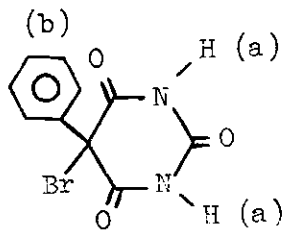
Table 6

NMR Shift Values in Units of δ For Derivatives of

5-Phenylbarbituric Acid as observed in DMSO-d_6.*



(a)	(b)	(c)	(d)
11.23 (singlet, 2H)	7.30 (singlet, 5H)	4.82 (singlet, 1H)	-
(e)	(f)	(g)	(h)



(a)	(b)	(c)	(d)
11.93 (singlet, 2H)	7.47 (singlet, 5H)	-	-
(e)	(f)	(g)	(h)

Table 6 Con't

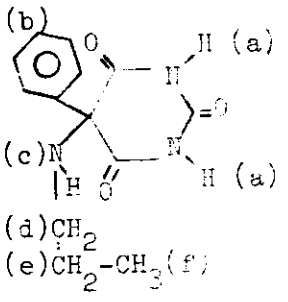
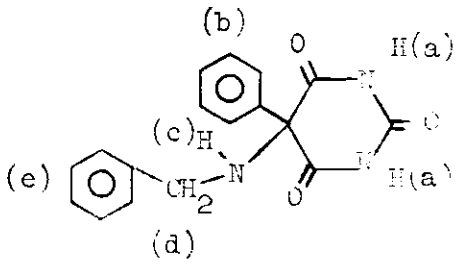
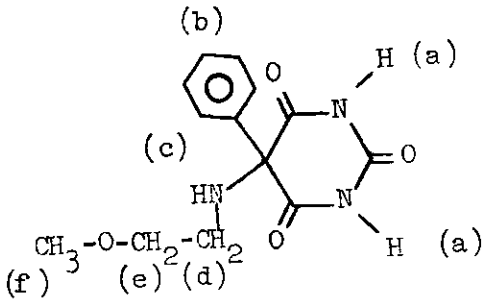
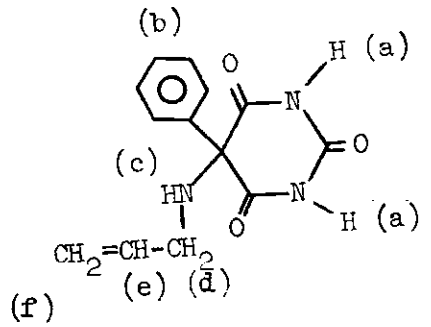
	(a) 10.93 (singlet, 2H)	(b) 7.42 (singlet, 5H)	(c)	(d) 2.42 (triplet, 2H)
	(e) 1.47 (multiplet, 2H	(f) 1.17 (triplet, 3H)	(g) -	(h) -
	(a) 11.70 (singlet, 2H)	(b) 7.40 (singlet, 5H)	(c) 3.23 (singlet, 1H)	(d) 3.73 (singlet, 2H)
	(e) 7.50 (singlet, 5H)	(f) -	(g) -	(h) -

Table 6 Con't



(a)	(b)	(c)	(d)
11.67 (singlet, 2H)	7.45 (singlet, 5H)		2.78 (triplet, 3H)
(e)	**(f)**	**(g)**	**(h)**
3.43 (triplet, 3H)	3.18 (singlet, 2H)		



(a)	(b)	(c)	(d)
11.67 (singlet, 2H)	7.29 (singlet, 5H)		3.04 (multiplet, 2H)
(e)	**(f)**	**(g)**	**(h)**
3.43 (multiplet, 1H)	5.00 (doublet, 2H)	-	-

Table 6 Con't

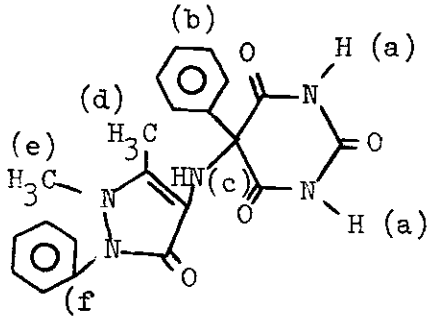
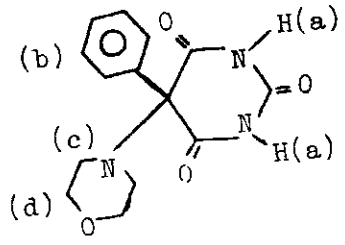
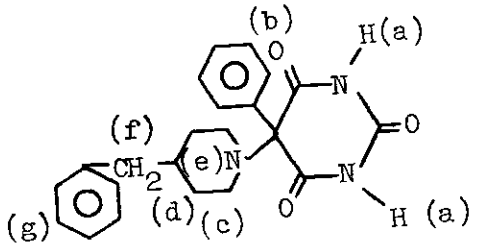
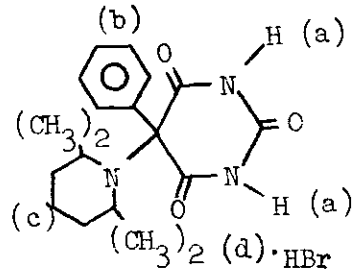
	(a) 10.96 (singlet, 2H)	(b) 7.37 (singlet, 5H)	(c) 5.13 (singlet, 1H)	(d) 2.67 (singlet, 3H)
	(e) 2.03 (singlet, 3H)	(f) 7.27 (singlet, 5H)	(g) -	(h) -
	(a) 11.67 (singlet, 2H)	(b) 7.50 (singlet, 5H)	(c) 2.63 (broad multi-plet, 4H)	(d) 3.60 (broad multi-plet, 4H)
	(e) -	(f) -	(g) -	(h) -

Table 6 Con't



(a)	(b)	(c)	(d)
11.77 (singlet, 2H)	7.53 (singlet, 5H)	2.37 (broad multiplet, 7H)	1.45 (broad multiplet, 4H
(e)	(f)	(g)	(h)
2.37 (broad multiplet, 7H)	2.37 (broad multiplet, 7H)	7.31 (singlet, 5H)	



(a)	(b)	(c)	(d)
9.46 (singlet, 2H)	7.45 (singlet, 5H)	1.57 (singlet, 6H)	1.47 (singlet, 12H)
(e)	(f)	(g)	(h)
-	-	-	-

Table 6 Con't

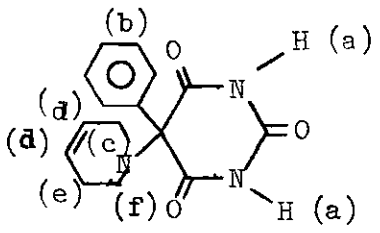
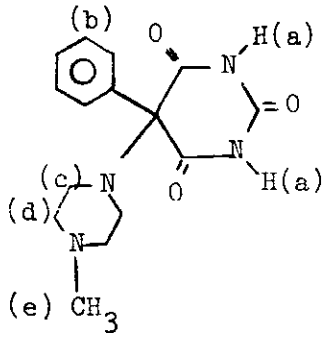
	(a) 11.68 (singlet, 2H)	(b) 7.47 (singlet, 5H)	(c) 3.15 (broad multiplet, 2H)	(d) 5.38 (multiplet, 2H)
	(e) 2.70 (broad multiplet, 2H)	(f) 2.07 (broad multiplet, 2H)	(g) -	(h) -
	(a) 8.50 (singlet, 2H)	(b) 7.42 (singlet, 5H)	(c) 2.58 (broad singlet, 4H)	(d) 2.35 (broad singlet, 4H)
	(e) 2.13 (singlet, 3H)	(f) -	(g) -	(h) -

Table 6 Con't

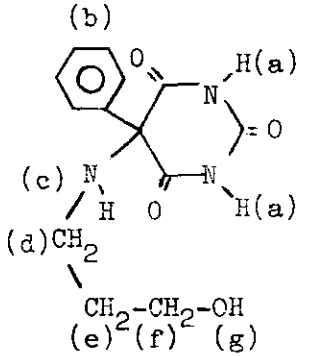
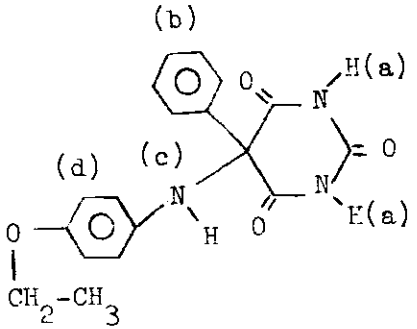
	(a) -	(b) 7.43 (singlet, 5H)	(c) -	(d) 1.67 (multiplet, 2H)
	(e) 2.52 (multiplet, 2H)	(f) 3.50 (triplet, 2H)	(g) -	(h) -
	(a) 11.83 (singlet, 2H)	(b) 7.52 (singlet, 5H)	(c) 6.35 (singlet, 1H)	(d) 6.63 (multiplet, 4H)
	(e) 3.88 (quartet, 2H)	(f) 1.27 (triplet, 3H)	(g) -	(h) -

Table 6 Con't

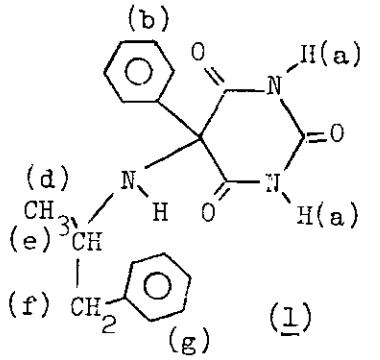
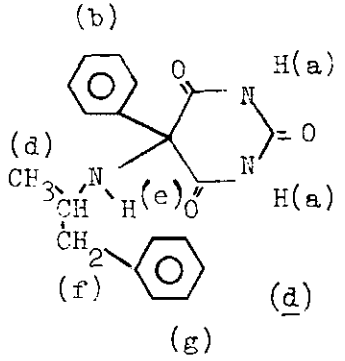
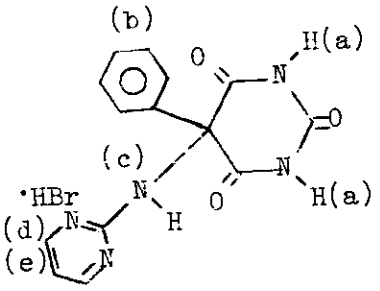
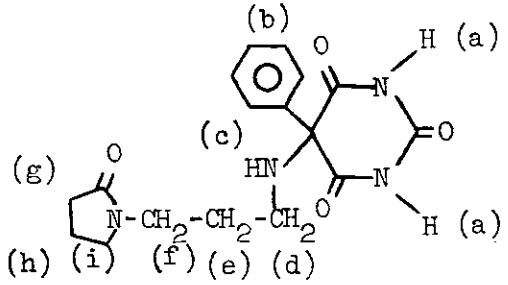
 (1)	(a) 10.92 (singlet, 2H)	(b) 7.47 (singlet, 5H)	(c) 2.80 (multiplet, 4H)	(d) 0.33 (doublet, 3H)
	(e) 2.80 (multiplet, 4H)	(f) 2.80 (multiplet, 4H)	(g) 7.20 (singlet, 5H)	(h) -
 (d)	(a) 10.92 (singlet, 2H)	(b) 7.47 (singlet, 5H)	(c) 2.80 (multiplet, 4H)	(d) 0.33 (doublet, 3H)
	(e) 2.80 (multiplet, 4H)	(f) 2.80 (multiplet, 4H)	(g) 7.20 (singlet, 2H)	(h) -

Table 6 Con't



(a)	(b)	(c)	(d)
11.63 (singlet, 2H)	7.45 (singlet, 5H)	-	8.33 (doublet, 2H)
(e)	(f)	(g)	(h)
6.67 (triplet, 1H)	-	-	-



(a)	(b)	(c)	(d)
11.53 (singlet, 2H)	7.32 (singlet, 5H)		2.37 (multiplet, 2H)
(e)	(f)	(g)	(h)
1.47 (multiplet, 2H)	3.07 or 3.17 (triplet, 2H)	1.92 (triplet, 2H)	~1.78 (multiplet, 2H)
(i)			
3.07 or 3.17 (triplet, 2H)			

Table 6 Con't

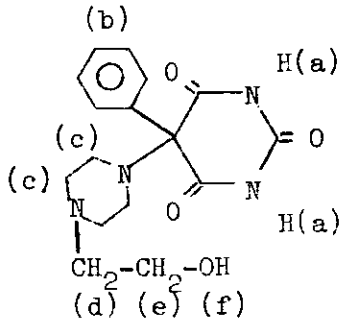
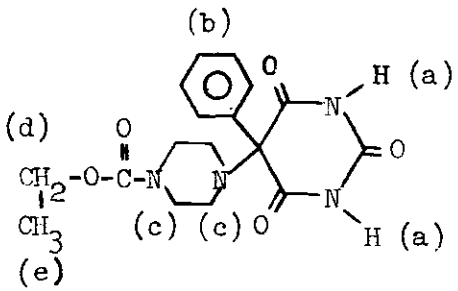
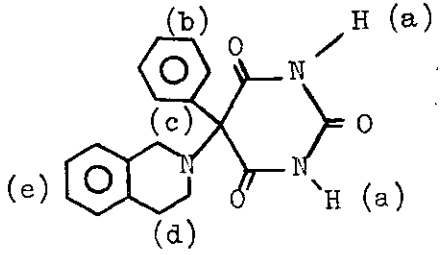
	(a) 8.00 (broad singlet , 2H)	(b) 7.43 (singlet, 5H)	(c) 2.48 (broad multiplet, 10H)	(d) 2.48 (broad multiplet, 10H)
	(e) 3.50 (triplet, 2H)	(f) -	(g) -	(h) -
	(a) 11.50 (broad singlet , 2H)	(b) 7.33 (singlet, 5H)	(c) 3.23 (broad multiplet, 8H)	(d) 3.90 (quartet, 2H)
	(e) 1.07 (triplet, 3H)	(f) -	(g) -	(h) -

Table 6 Con't

	(a) 11.73 (singlet, 2H)	(b) 7.50 (singlet, 5H)	(c) 3.83 (doublet, 2H)	(d) 1.15 (broad multi-plet, 4H)
	(e) 7.13 (broad multi-plet, 4H)	(f) -	(g) -	(h) -

*
TMS was employed as an internal reference in all cases.

Rapid exchange of the NH proton of the amine apparently occurs in nearly all cases observed. In the two benzyl amine derivatives the NH proton of the amine was observed at 2.45 δ and 3.23 δ , respectively, in the 5-ethylbarbiturate and the 5-phenylbarbiturate. The amine proton of the 5-phenyl-5-[N-(p-phenetidine)]-barbituric acid was seen at 6.35 δ due to deshielding by the two phenyl groups. The NH proton of the amine portion in the two amphetamine derivatives appears as part of an unresolved multiplet centered at 2.80 δ . The spectrum of the two barbituric acid derivatives of 4-aminoantipyrene is exceptional in that both the imide hydrogens and the amine hydrogen in the ethyl and the phenyl case appear as sharp singlets. In the ethyl case, the imide hydrogens appear at 10.85 δ and the amine hydrogen at 4.87 δ. In the phenyl case, the imide hydrogens appear at 10.96 δ and the amine hydrogen at 5.13 δ .

The 5-phenyl-5-[N-(2-aminopyrimidino)]-barbituric acid salt which was obtained has an unusual NMR spectrum.

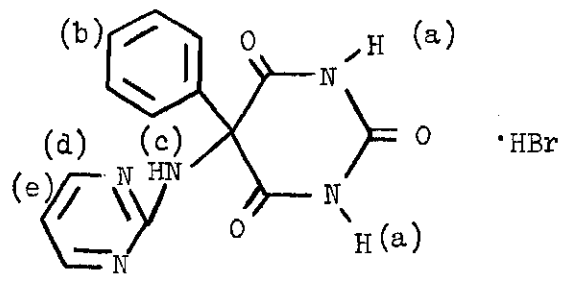


Figure 17. 5-Phenyl-5-[N-(2-aminopyrimidino)]-barbitruic Acid Salt

The two (d) protons which appear as a doublet on dissolving in dimethyl sulfoxide-d_6 appeared as two doublets on allowing the sample to stand overnight in the solvent. The second doublet appears at slightly lower field. The ratio of the integrals of the higher field doublet to that of the lower field doublet is ca. 1.6 to 1. The (e) proton which initially appears as a triplet became two triplets with the second triplet again appearing at slightly lower field. In addition, two singlets, each integrating for less than one proton, appear at 8.83 δ and 8.33 δ , respectively. These observations may indicate that the two nitrogens of the pyrimidine ring are no longer equivalent after standing in solvent. This could be explained by assuming that the proton of the salt resides initially on the same hydrogen as the (c) proton. But, on standing, one of the nitrogens of the pyrimidine ring is protonated.

Mass Spectrometry of the Phenyl Derivatives

The use of mass spectrometry was found to be extremely beneficial in establishing that a covalent bond existed between the C_5 carbon and the nitrogen of the amine in the compounds prepared. Of particular significance were peaks found at 104 and 103 in the 5-phenyl derivatives. These ion fragments are depicted in Figure 18.

One or the other or both were shown by all of the phenyl derivatives except the hydrobromide of 5-phenyl- [N-(2,2,6,6-tetramethylpiperidino)]-barbituric acid in relative abundances ranging from 5 per cent to 100 per cent of the base peak. The cases in which this ion

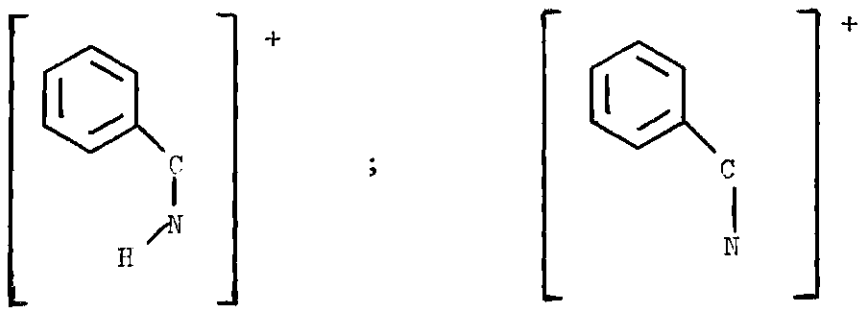


Figure 18. m/e 104 and m/e 103

was also the base peak are shown in Figure 19.

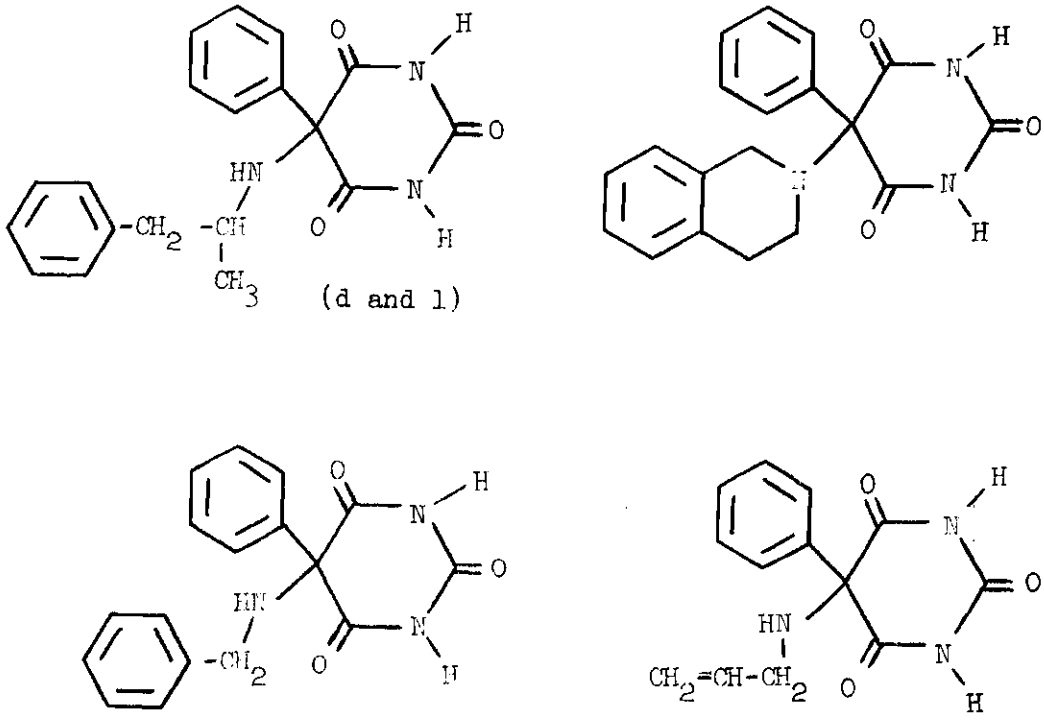


Figure 19. Molecules Having Base Peak at m/e 104.

In 5-phenyl-5-[N-(p-phenetidino)]-barbituric acid (m.w. 339) a fragment occurs at m/e 297 which may be attributed to loss of $-\overset{O}{\overset{\|}{C}}-N-$ with concomitant hydrogen transfer from nitrogen to the adjacent carbonyl oxygen of the ion observed or by loss of this group from an enolic form of the compounds. Other fragments occur at 225 and 224 which are probably due to fragment(s) in Figure 20 where hydrogen is transferred to give the ion of lower mass. Another fragment frequently seen resulted from loss of $-\overset{H}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-N$ to give an M-57 peak.

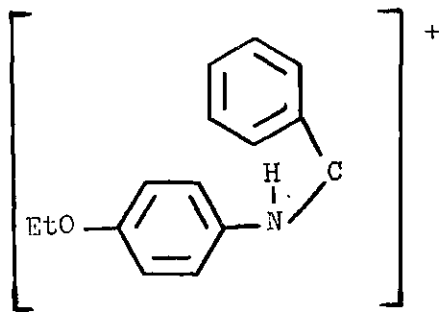


Figure 20. m/e 225

In a number of the nineteen new phenylbarbituric acid derivatives prepared, molecular ions were observed in the mass spectrum. These ions varied in abundance from 5 per cent to 55 per cent of the base peak.

McLafferty rearrangement[14] via cleavage of the amine to give the fragment shown in Figure 21 occurred in all phenyl cases except the one in which the amine portion was N-3(aminopropyl)-2-pyrrolidine.

The relative abundance of these ions varied from 6 per cent to 100 per cent of the base peak. The latter case was observed when the amine portion was 3-amino-1-propanol. This amine cleavage apparently may occur through either a five or a six membered ring.

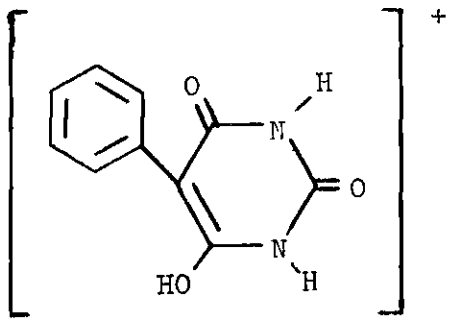


Figure 21. m/e 204

Frequently a fragment corresponding to that shown in Figure 22 occurred (m/e 174). These fragments varied from 4 per cent to 31 per cent of the base peak.

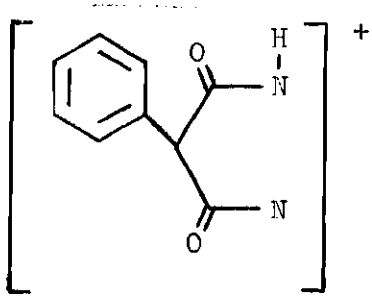


Figure 22. m/e 174

In all cases (except where the amine was ethyl N-piperazinocarboxylate) a peak occurred at m/e 132 corresponding to further fragmentation of the barbituric acid ring. The relative abundance of these peaks ranged from 7 per cent to 52 per cent. This fragment is depicted in Figure 23.

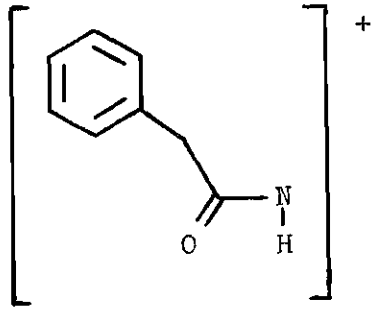


Figure 23. m/e 132

All of the derivatives of phenylbarbituric acid prepared gave ions at m/e 117 or m/e 118 shown in Figure 24. These ions varied in relative abundance from 6 per cent to 100 per cent of the base peak. The latter case occurred when the amine portion was the N- β-hydroxyethylpiperazino group.

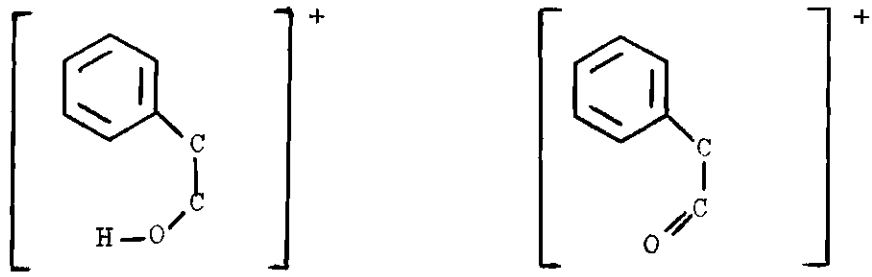


Figure 24. m/e 118 and m/e 117

Mass Spectrometry of the Ethyl Derivatives

A fragment occurred in the ethyl derivatives at m/e 56 and m/e 55 (similar to that occurring in the phenyl derivatives at m/e 104 and m/e 103) and is shown in Figure 25. The only ethyl derivatives not giving this peak was 5-ethyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric acid. However, this compound did give an M-1 peak at m/e 286 and M-29 peak. The latter was also given by over half the ethyl derivatives.

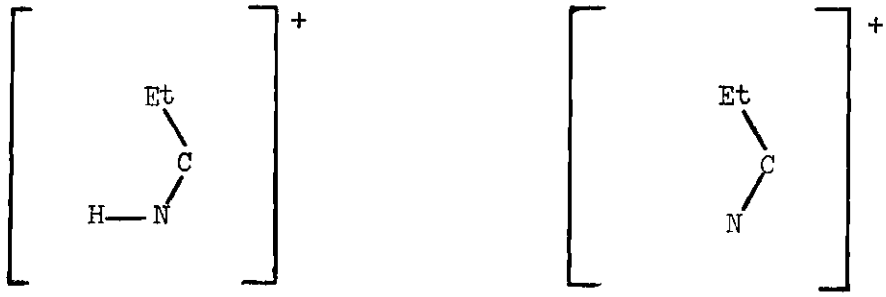


Figure 25. m/e 56 and m/e 55

Fragments similar to that depicted (MW = 339) in Figure 20 (for the phenyl case) were $-\overset{O}{\overset{\|}{C}}-N$ was lost were also observed for the ethyl derivatives.

Six of the derivatives of ethylbarbituric acid gave molecular ions. The relative abundance of these ions varied from 4 per cent to 100 per cent of the base peak. This peak was also the base peak in the case of 5-ethyl-5-[N-(4-aminoantipyreno)]-barbituric acid. Two additional compounds gave M-1 peaks.

In only two cases were M^+ or $(M-1)^+$ peaks not given. For 5-ethyl-5[N-(ethyl-N-piperazinocarboxylato)]-barbituric acid the heaviest ion seen corresponded to M-29 while for the N-β-hydroxyethyl piperazine derivative the peak corresponded to M-30 (an M-31 peak was also seen).

In half the ethyl cases, a McLafferty rearrangement was again observed to give m/e 156. In the case of 5-ethyl-5-[N-piperazinocarboxylato)]-barbituric acid this peak was also the base peak.

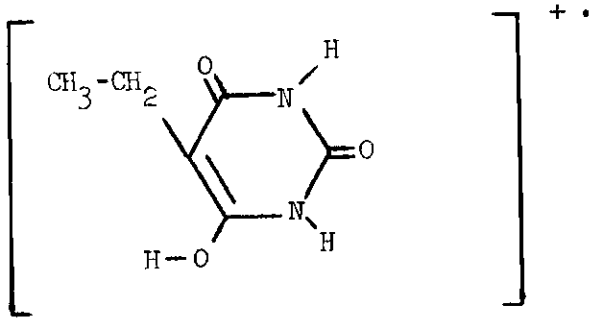


Figure 26. m/e 156

In several ethyl cases fragmentation by allylic cleavage and loss of a methyl radical occurred to give a peak at m/e 141. In one instance this was also the base peak. This behavior is analogous to that observed in 1,3-diketones.[51]

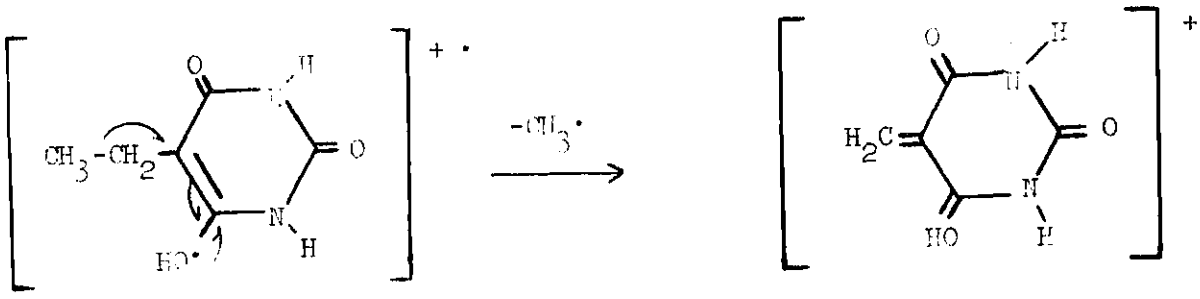


Figure 27. Cleavage of a Methyl Radical

A second McLafferty rearrangement is also possible for the 5-ethylbarbituric acid derivatives and this was observed in more than half of the compounds prepared.

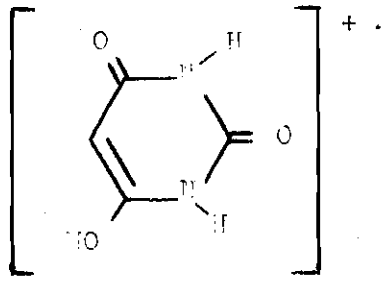


Figure 28. m/e 128

A fragment occurs at m/e 98 in more than one-half of the cases

observed as does a peak at m/e 85 and m/e 83. Possible structures for these fragments are depicted in Figure 29. The peak at m/e 98 has a relative abundance of as much as 90 per cent of the base peak in one case.

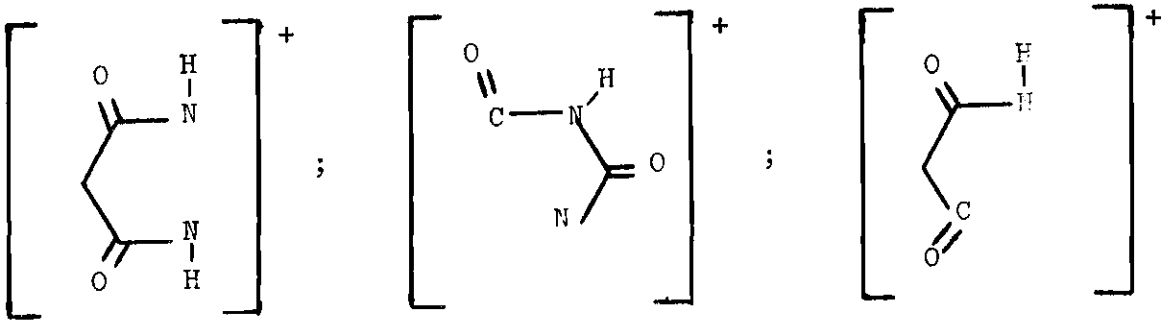


Figure 29. m/e 98, m/e 85, m/e 83

The types of specific fragmentations observed in this study could greatly aid the identification of barbiturates in general. The microgram sensitivity of mass spectrometers renders mass spectrometry a puissant tool in forensic analysis.

The mass spectrum of the 5-phenyl- [N-(2,2,6,6-tetramethyl-piperidino)] barbituric acid salt is unique in that it does not show the peaks at m/e 104 or m/e 103 which were observed for all other phenyl derivatives. The heaviest ion observed is at m/e 204 and no evidence of the presence of bromine is seen in the mass spectrum. The infrared spectrum showns an intense band at 1559 cm^{-1} which was observed to occur in salts of these compounds. The ultraviolet spectrum does not reveal a band above end absorption in neutral media.

Although the elemental analysis clearly shows that a salt does exist, it is not possible to form further conclusions from the data available.

CHAPTER III

EXPERIMENTAL

All melting points are recorded in degrees Centigrade and are uncorrected. Melting points were determined in capillary tubes of 1.5-2.0 mm (OD), by heating in an aluminum block at a rate of 1-2° per minute. To insure consistency, the same thermometer was used for all melting point determinations. Elemental microanalyses were performed by Atlantic Micro-Laboratories, Atlanta, Georgia. Infrared spectra employing potassium bromide pellets were recorded using a Perkin-Elmer Model 700 spectrophotometer. Ultra-violet spectra were recorded using a Cary Model 14 Recording Spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60D spectrometer. Mass spectral data was obtained using either a Varian Model M-66 mass spectrometer or a Hitachi Perkin-Elmer RMU-7L mass spectrometer.[6] Optical rotations were determined using a Bendix Ericsson-NPL Model 968 automatic polarimeter. All pH measurements were on a Coleman Model 28C pH meter.

5-Ethylbarbituric Acid

The general procedure of Dickey and Gray[24] was used with modifications. In a three-necked, five liter round-bottom flask fitted with a dropping funnel, a condenser (to which was affixed a calcium chloride drying tube), a mechanical stirrer, and a heating mantle, 34.5 g (1.5 mole) of freshly cut sodium was reacted with 3 l of anhydrous absolute

ethanol. To the ethoxide solution was slowly added, over a period of 30 minutes 282.0 g (1.5 mole) of diethyl ethylmalonate and the mixture was allowed to cool to room temperature. In several portions was added 90.0 g (1.5 mole) of solid urea.

Vigorous stirring was commenced and heat was applied to the reaction mixture. A short time after heating was begun a white precipitate appeared. The reaction mixture was brought slowly to the reflux temperature and refluxed with continued stirring for 4.5 hours. Ethanol removal by distillation was begun at this time and continued until approximately one and one-half liters had been removed. At this time, 1370 ml of water and 130 ml of concentrated hydrochloric acid was added. The solution became clear at this point and distillation was continued until a total volume of 3 l of ethanol had been removed. The remaining hot solution was poured into a 2 l Erlenmeyer flask and placed in the refrigerator overnight. The 5-ethylbarbituric acid which precipitated was removed by filtration and washed twice with 300 ml portions of distilled water. The white crystals were then placed in the vacuum desiccator to dry. The yield was 184.0 g (78 per cent), m.p. 188-190° (lit (2) m.p. 189-190°).

The IR shows carbonyl bands at 1720 cm^{-1} (strong) and 1700 cm^{-1} (strong). The UV spectrum of this compound taken in 0.3 N NaOH in 95 per cent ethanol showed absorptions at λ_{max} 229 nm (ϵ5,760) and λ_{max} 269 nm (ϵ12,500). The NMR spectrum (DMSO-d_6) showed bands at 11.23 δ (singlet, 2H), 3.53 δ (multiplet, 1H) and 1.90 δ (multiplet, 2H), and 0.83 δ (triplet, 3H). The mass spectrum gave the expected molecular ion, M^+ 156 (calculated M^+ = 156).

5-Bromo-5-ethylbarbituric Acid

This procedure was based upon that of Cox, et al.[16] who had reported the synthesis of 5-bromobarbituric acids. In a typical experiment, 173.0 g (1.11 mole) of 5-ethylbarbituric acid was dissolved in 1 l of water near the boiling point. With stirring and continued heating, bromine was added slowly until a yellow color persisted. The bromine color was then dissipated by the addition of sodium bisulfite. The solution was then chilled and filtered. The solid obtained was recrystallized from water and dried seventy-two hours in the vacuum desiccator to give 200.0 g (77 per cent yield) of white crystals, m.p. 203-205, (lit (21) m.p. 202°).

The IR spectrum showed carbonyl absorptions at 1760 cm^{-1}, 1725 cm^{-1}, and 1700 cm^{-1} (all strong). The NMR (DMSO-d_6) showed bands at 11.82 δ (singlet, 2H), 2.33 δ (quartet, 2H), 0.83 δ (triplet, 3H). The mass spectrum showed peaks at m/e 205 and m/e 207 corresponding to loss of ethyl, but no molecular ion (calculated m/e = 234,236).

5-Ethyl-5-[N-(benzylamino)]-barbituric Acid

In a 100 ml, round-bottomed flask equipped with a condenser and calcium chloride drying tube, was introduced 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid. This was followed by addition of 40 ml of methanol. When the solid was completely dissolved, 9.0 g (0.084 mole) of freshly distilled benzylamine at once was added and magnetically stirred. Refluxing was commenced and continued for one hour. At this time, the reaction was cooled and the pH observed to be 8.2. The pH was then adjusted to 11.3 by addition of 0.6 N aqueous

NaOH monitoring the pH charges on a pH meter and the mixture extracted with 40 ml of benzene. On acidification of the alkaline layer with aqueous HCl, a finely divided white precipitate separated. This was filtered, washed with cold water, and dried. The solid was then boiled in 100 ml of water and filtered while hot. It was then dried in an Abderhalden drying pistol utilizing refluxing benzene. The white crystalline product weighed 6.8 g (61 per cent yield), m.p. 217-218°.

Significant IR absorptions were found at 3390 cm^{-1} (medium, shoulder), 1750 cm^{-1} (strong), and 1718 cm^{-1} (sharp). The UV spectrum in 0.3 N NaOH in 95 per cent ethanol showed λ_{max} 226 nm (ϵ, 13,900) and λ_{max} 260 (ϵ, 6340). The NMR spectrum in DMSO-d_6 showed absorptions at 11.52 δ (singlet, 2M), 7.23 δ (quartet, 2H), and 0.73 δ (triplet, 3H). The mass spectrum showed $(M-29)^+$ (CH_3-CH_2-) at 232. (Calculated mass = 261). Calculated for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.61; H, 5.78; N, 15.98.

5-Ethyl-5-[N-(4-benzylpiperidino)]-barbituric Acid

Five grams (0.021 mole) of 5-bromo-5-ethylbarbituric acid was dissolved in 20 ml of methanol and while the solution was stirred magnetically 7.4 g (0.042 mole) of 4-benzylpiperidine was added. The solution was then refluxed for one hour and cooled. When no precipitate was visible, the solvent was removed on the rotating evaporator and precipitation induced by vigorously shaking the resultant tar with water. The solid was then removed by filtration and dried. Recrystallization was effected from an ethanol-water mixture, m.p. 215-216°, 5.1 g (73 per cent yield). An analytical sample was prepared by a second

recrystallization (as above) and drying overnight at 80° in vacuo.

The IR spectrum showed carbonyl absorptions at 1760 cm^{-1} (strong) and 1690 cm^{-1} (strong). The UV spectrum recorded in 95 per cent ethanol which was 0.3 N in NaOH showed bands at λ_{max}226 nm, (ε, 14,800) and λ_{max}261 nm, (ε,7,060). The NMR spectrum (DMSO-d_6) showed absorptions at 11.33 δ (doublet, 2H), 7.06 δ (singlet, 5H), 2.72 δ (multiplet, 4H), 2.37 δ (doublet, 2H), 2.13 δ (multiplet, 4H), 1.78 δ (multiplet, 2H), 1.30 δ (multiplet, 1H), 0.63 δ (triplet, 3H). The mass spectrum showed a molecular ion at 329 (calculated = 329). Calculated for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76; Found: C, 65.70; H, 7.13; N, 12.79.

5-Ethyl-5-[N-(morpholino)]-barbituric Acid

To a solution of 5.0 g (0.021 mole) of 50 bromo-5-ethylbarbituric acid in 20 ml of methanol contained in a 100 ml round-bottomed flask equipped with a condenser and a calcium chloride drying tube was added 3.7 g (0.042 mole) of freshly distilled morpholine. The solution was then brought to the reflux temperature and refluxed for one hour while the solution was stirred magnetically. This mixture was then cooled and approximately one-half of the solvent was removed on the rotovap in order to concentrate the precipitate which was visible. At this time the solid which had formed was removed by filtration under reduced pressure, washed and distilled with water and dried. The precipitate was then recrystallized from the minimal amount of boiling 95 per cent ethanol and dried at 80° for seventy-two hours under 1 mm pressure. The white solid weighed 4.2 g (82 per cent yield), m.p. 239-240°.

The IR showed an absorption at 1710 cm^{-1} (strong, broad). The UV spectrum taken in 0.3 N NaOH in 95 per cent ethanol showed λ_{max}226 nm, (ε, 17,300) and λ_{max}262 nm, (ε,1,400). The NMR spectrum (DMSO-d_6) gave absorptions at 11.37 δ (singlet, 2H), 3.42 δ (singlet, 4H), 2.42 δ (singlet, 4H), 1.80 δ (quartet, 2H), and 0.60 δ (triplet, 3H). The mass spectrum showed a peak at m/e 241 (calculated, 241). Calculated for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.81; H, 6.28; N, 17.33.

5-Ethyl-5-[N-(ethylisonipecotato)]-barbituric Acid

Ethyl isonipecotate (13.2 g, 0.084 mole) was added to a solution of 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid in 40 ml of methanol. The mixture was mechanically stirred in a 100 ml round-bottomed flask equipped with a condenser and calcium chloride drying tube. After refluxing for one hour, the solvent was removed on the rotovap to give a red resinous material from which crystallization was effected by prolonged shaking with water. The solid was removed by filtration under vacuum, washed with distilled water and dried. Recrystallization from 95 per cent ethanol and drying overnight at 80° under vacuum yielded a white solid, m.p. 189-190° (weighing 4.1 g) (31 per cent yield). It should be noted that this product is somewhat soluble in 95 per cent ethanol and a significant amount (ca. 30 per cent) is lost on recrystallization.

The IR spectrum showed significant carbonyl absorptions at 1740 cm^{-1} (shoulder), 1710 cm^{-1}(shoulder) and 1690 cm^{-1} (strong). The UV spectrum taken in 0.3 N NaOH in 95 per cent ethanol showed λ_{max}226 nm, (ε,16,400) and λ_{max}262 nm, (ε,9,960). The NMR spectrum

in DMSO-d_6 gave bands at 11.50 δ (singlet, 2H), 4.03 δ (quartet, 2H), 2.50 δ (multiplet, 4H), 1.80 δ (quartet, 2H),1.73 δ (multiplet, 5H), 1.15 δ (triplet, 3H), and 0.72 δ (triplet, 3H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 53.97; H, 6.88; N, 13.47.

5-Ethyl-5-[N-(4-methylpiperazino)]-barbituric Acid

A solution prepared from 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid, 8.4 g (0.084 mole) of N-methylpiperazine (freshly distilled) and 40 ml of methanol was mechanically stirred in a 100 ml round-bottomed flask fitted with a condenser and a calcium chloride drying tube. This mixture was then heated and brought to the reflux temperature. Refluxing was continued for one hour and then part of the solvent was evaporated and the solution was filtered through sintered glass under reduced pressure, washed with copious quantities of distilled water, and dried. Recrystallization was effected from an ethanol-water mixture. The solid was dried overnight in an Abderhalden drying pistol utilizing refluxing benzene and a pressure of 1 mm, m.p. 283-284°. This reaction gave 3.3 g (31 per cent yield) of pure product.

The IR spectrum showed significant bands, for the carbonyl at 1690 cm^{-1} (strong, broad) and a band at 1600 cm^{-1} (strong) which could be attributed to N-H bending. The UV spectrum in 0.3 N NaOH in 95 per cent ethanol gave λ_{max}226 nm, (ε,18,600) and λ_{max}262 nm, (ε,11,300). The NMR (DMSO-d_6) showed absorptions at 2.38 δ (singlet, 4H), 2.20 δ (singlet, 4H), 1.90 δ (singlet, 3H), 1.77 δ (quartet, 2H), and 0.60 δ

(triplet, 3H). The mass spectrum gave a molecular ion at 254.1391 Calculated for $C_{11}H_{18}N_4O_3$: C, 51.96; H, 7.13; N, 22.03. Found: C, 51.79; H, 7.22; N, 21.92.

5-Ethyl-5-[N-(4-β-hydroxyethylpiperazino)]-barbituric Acid

A solution was prepared by dissolving 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid in 40 ml of methanol and adding 11.0 g (0.084 mole) of N-β-hydroxyethylpiperazine while stirring constantly in a 100 ml round-bottomed flask equipped with a condenser and a calcium chloride drying tube. Heat was observed to be evolved on mixing. The solution was then refluxed for one hour and cooled to room temperature. The precipitate which was visible was removed by suction filtration through a fritted disc, washed with distilled water and air dried. It was recrystallized from distilled water to which a small amount of ethanol had been added. An analytical sample was prepared by a similar recrystallization and drying overnight at 80° under ca. 1 mm of pressure, 264-265°, 4.6 g (38 per cent yield).

The IR spectrum showed absorptions for OH stretch at 3450 cm^{-1} (medium) and for carbonyl at 1700 cm^{-1} (strong). The UV spectrum in 0.3 N NaOH in 95 per cent ethanol revealed bands of λ_{max} 225 nm, (ε, 15,400) and λ_{max} 262 nm, (ε,7,080). The NMR spectrum (DMSO-d_6) showed absorptions at 11.33 δ (singlet, 2H), 3.50 δ (triplet, 2H), 2.42 δ (multiplet, 8H), 2.33 δ (triplet, 2H), 1.95 δ (quartet, 2H), and 0.72 δ (triplet, 3H). No molecular ion was observed. Calculated for $C_{12}H_{20}N_4O_4$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.83; H, 7.12; N, 19.64.

5-Ethyl-5-[N-(Ethyl-N-piperazinocarboxylato)]-barbituric Acid

A solution of 10.0 g (0.042 mole) of 5- bromo-5-ethylbarbituric acid, 13.2 g (0.084 mole) of redistilled ethyl N-piperazinocarboxylate, and 40 ml of methanol was stirred with heating under reflux for one hour, after which the solvent was removed on the rotovap. The resultant red tar was shaken with a mixture of 75 ml of diethyl ether and 30 ml of acetone. The precipitate which formed was removed by filtration under reduced pressure and dried. The solid was then stirred into 60 ml of 0.6 N aqueous NaOH and extracted with a like volume of benzene. The alkaline layer was then acidified with HCl. When no precipitate was visible ca. one-half of the solvent was removed on the rotovap and the remaining solution placed in the refrigerator overnight. A precipitate formed which was removed by filtration and dried. Recrystallization was then accomplished from 95 per cent ethanol. The solid was then dried overnight at 80° under vacuum, m.p. 160-161°, 4.2 g (32 per cent yield).

The IR spectrum showed carbonyl bands at 1750 cm^{-1} (strong) and 1680 cm^{-1} (strong, broad). The UV spectrum in 0.3 N NaOH in 95 percent ethanol showed absorptions at λ_{max}225 nm, (ϵ, 15,700) and λ_{max}262 nm, (ϵ, 7,340). The NMR spectrum (DMSO-d_6) gave bands at 11.57 δ (singlet, 2H), 4.03 δ (quartet, 2H), 3.32 δ (singlet, 4H), 2.85 δ (singlet, 4H), 1.88 δ (quartet, 2H), 1.13 δ (triplet, 3H), and 0.77 δ (triplet, 3H) in DMSO-d_6. The mass spectrum did not reveal a molecular ion. Calculated for $C_{13}H_{20}N_4O_5$: C, 49.99; H, 6.45; N, 17.94. Found: C, 50.03; H, 6.56; N, 17.79.

5-Ethyl-5-[N-(N'-3-(aminopropyl)-2-pyrrolidinono)]-barbituric Acid

In 40 ml of methanol was dissolved 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid. Stirring was continued and 12.0 g (0.084 mole) of N-3(aminopropyl)-2-pyrrolidinone was added. Evolution of heat was observed on mixing. The mixture was then refluxed for one hour and cooled. The solvent was then removed on the rotovap and a solid was crystallized by vigorous shaking with water. This solid was removed by filtration and washed with water. Recrystallization was effected from distilled water and the white solid was dried under vacuum in an Abderhalden drying pistol at 80° and ca. 1 mm of pressure, m.p. 251-252°, 3.1 g (25 per cent yield).

The IR spectrum showed significant bands and carbonyl bands at 3300 cm^{-1} (weak), N-H stretch; 1740 cm^{-1} (shoulder), 1700 cm^{-1} (strong), and 1660 cm^{-1} (strong). The UV spectrum in 0.3 N NaOH in 95 percent ethanol showed λ_{max}225 nm (ϵ,15,900) and λ_{max}259 nm (ϵ 7,560). The NMR spectrum in (DMSO-d_6) gave absorptions at 11.48 δ (singlet, 2H), 3.17 δ (triplet, 2H), 1.85 δ (multiplet, 2H), 1.70 δ (quartet, 2H), 1.42 δ (multiplet, 2H), and 0.65 δ (triplet, 3H). The mass spectrum gave a molecular ion at 296 (calculated, 296).
Calculated for $C_{13}H_{20}N_4O_4$: C, 52,69; H, 6.80; N, 18,91.
Found: C, 52.81; H, 6.88; N, 1880.

5-Ethyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)]-barbituric Acid.

In 40 ml of methanol contained in a 100 ml round-bottomed flask equipped with a condenser and a calcium chloride drying tube was dissolved 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid. The solution was stirred while 11.2 g (0.084 mole) of freshly distilled

1,2,3,4-tetrahydroisoquinoline was added The resultant solution was refluxed for one hour and cooled. The solid present was removed by filtration, washed with water, and dried. It was then recrystallized twice from an ethanol-water mixture and dried overnight at 80° under a pressure of 1 mm. The yield of slightly off-white crystals was 4.8 g (39 per cent yield), m.p. 281-282°.

The IR spectrum showed carbonyl absorptions at 1760 cm^{-1} (strong) and 1690 cm^{-1} (strong). The UV spectrum recorded in 0.3 N NaOH in 95 percent ethanol showed the usual bands at λ_{max}226 nm, (ε,17,200) and λ_{max}263 nm, (ε 9,180). The NMR spectrum in (DMSO-d_6) showed absorptions at 9.08 δ (singlet, 2H); 6.81 δ (singlet, 2H); 4.12 δ (singlet, 1H); 3.70 δ (singlet, 1H); 3.23 δ (multiplet, 2H); 2.80 δ (multiplet, 2H); 1.77 δ (quartet, 2H); 0.68 δ (triplet, 3H). The mass spectrum showed a molecular ion at 287 (calculated, 287). Calculated for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.66; H, 6.02; N, 14.53.

5-Ethyl-5-[N-(4-aminoantipyreno)]-barbituric Acid

A mixture of 10.0 g (0.042 mole) of 5-bromo-5-ethylbarbituric acid, 17.0 g (0.042 mole) of 4-aminoantipyrene and 60 ml of methanol was stirred together in a 100 ml boiling flask fitted with a condenser and calcium chloride drying tube. A deep violet color formed as the amine was added and heat was evolved. The solution was refluxed for one hour, then cooled, and the solvent removed on the rotary evaporator. The resultant red tar was stirred with a mixture of water and acetone overnight. A yellow solid had formed the following morning which was removed by filtration and air dried. An unsuccessful attempt was made

to decolorize this compound with decolorizing charcoal. It was then recrystallized twice from an ethanol-water mixture and dried for seventy-two hours at 80° under vacuum, m.p. 233-234° (dec.), 5.4 g (36 percent yield).

The IR spectrum showed an absorption for N-H stretch at 3360 cm^{-1} (medium), carbonyl absorptions at 1740 cm^{-1} (strong) and 1700 cm^{-1} (strong) and an absorption at 1610 cm^{-1} (strong) attributed to N-H bending. The UV spectrum in 0.3 N NaOH in 95 per cent ethanol gave bands at 226 nm (ε,24,000) and λ_{max}256 nm (ε,14,400). The NMR spectrum (in trifluoroacetic acid) gave bands at 7.13 δ (multiplet, 5H), 3.12 δ (singlet, 3H), 2.11 δ (singlet, 3H), 1.68 δ (quartet, 2H), and 0.60 δ (triplet, 3H). The mass spectrum revealed a molecular ion at 357 (calculated, 357). Calculated for $C_{17}H_{19}N_5O_4$: C, 57.14; H, 5.36; N, 19.60. Found: C, 57.26; H, 5.53; N, 19.50.

5-Phenylbarbituric Acid

The general procedure of Dickey and Gray[24] was used with modifications. Into a three-necked five-liter round-bottomed flask fitted with a dropping funnel, a condenser to which was fitted a calcium chloride drying tube, a mechanical stirrer, and a heating mantle, 34.5 g (1.5 mole) of freshly cut sodium was reacted with 3 l of anhydrous absolute ethanol. To this ethoxide solution 354.0 g (1.5 mole) of diethyl phenylmalonate was slowly added over a period of 30 minutes and the mixture then was warmed slightly. In several portions was added 90.0 g (1.5 mole) of U.S.P. urea as a solid through an arm of the flask while vigorous stirring was continued. A dense white solid formed

and remained even at the reflux temperature. The solution was allowed to reflux for two and one-half hours and then ethanol removed by distillation. When approximately 1.5 liters of ethanol had been removed, 1370 ml of distilled water and 130 ml (ca. 1.5 mole) of concentrated HCl was added. The solution did not clear. Approximately 1.5 more liters of ethanol was removed by distillation and the hot solution placed in the refrigerator overnight to cool. The solid was then removed by filtration and washed with 1 l of the cold dilute acid above. This precipitate was then dried and placed in a 4 l beaker and stirred with 2 l of ethanol. This allowed removal of unreacted ester as the condensation product was virtually insoluble in ethanol. The 5-phenylbarbituric acid was then removed by filtration and dried for seventy-two hours in a vacuum desiccator, m.p. 257-259° (lit (59) 250°; lit (5) 263°); 230 g (73 per cent yield).

The IR spectrum showed two important bands at 1685 cm^{-1} (strong) carbonyl and 1500 cm^{-1} (strong), attributed to N-H bending. The UV spectrum in 95 per cent ethanol which was 0.3 N in NaOH showed λ_{max} 226 nm, (ϵ 7,880) and λ_{max} 271 nm, (ϵ 17,000). The NMR in DMSO-d_6 showed three bands: 11.22 δ (singlet, 2H), 7.30 δ (singlet, 5H), and 4.82 δ (singlet, 1H). The mass spectrum gave the expected molecular ion, m/e 204, (calculated mass = 204).

5-Bromo-5-phenylbarbituric Acid

The general procedure of Voorhes and Skinner[5] was used with modifications. In a typical reaction 30.0 g (0.147 mole) of 5-phenylbarbituric acid was dissolved in 250 ml of 0.6 N aqueous NaOH. Saturated bromine water was then added until the bromine color persisted.

Sodium bisulfite was then added to destroy the residual bromine and the solution was allowed to cool in the refrigerator overnight. The precipitate was then filtered and washed with copious amounts of distilled water. It was then dried seventy-two hours in a vacuum desiccator, m.p. 211-213° (lit (70) 214°), 36.5 g (88 per cent yield). The white crystalline product was used without further purification in all reactions.

The IR spectrum revealed three carbonyl bands at 1770 cm^{-1}, 1740 cm^{-1}, and 1690 cm^{-1} (all strong). The NMR spectrum (DMSO-d_6) showed two absorptions at 11.93δ (singlet, 2H) and 7.47 δ (singlet, 5H). The mass spectrum showed the expected bromine containing ions at m/e 282 and 284 with facile bromine cleavage (calculated m/e 282, 284).

5-Phenyl-5-[N-(n-propylamino)]-barbituric Acid

10 g (0.036 mole) of 5-bromo-5-phenyl barbituric acid was dissolved in 40 ml of methanol. To this solution was added 4.2 g (0.072 mole) of freshly distilled n-propylamine. Some evolution of heat was observed on addition of the amine. The mixture was then heated with reflux in a 100 ml round-bottom flask fitted with a condenser and a calcium chloride drying tube for one hour and cooled. Since only a small amount of precipitate was visible at this time the solution was concentrated by removal of ca. one-half of the solvent on a rotatory evaporator. The solid was then removed by filtration, dried and boiled with 100 ml of distilled water, filtering while hot. It was then dried overnight at 80° in vacuo, m.p. 180-181°, 8.5 g (92 per cent yield).

The IR spectrum showed two carbonyl absorptions at 1760 cm^{-1}

(strong) and 1700 cm^{-1} (strong). The UV spectrum in 0.3 N NaOH (95 per cent ethanol) showed two bands at λ_{max} 226 nm, (ϵ 18,00) and λ_{max} 261, (ϵ 6,520). The NMR spectrum recorded in dimethyl sulfoxide, showed absorptions at 10.93 δ (singlet, 2H), 7.42 δ (singlet, 5H), 2.42 δ (triplet, 2H), 1.47 δ (multiplet, 2H), and 1.17 δ (triplet, 3H). The mass spectrum showed the calculated molecular ion at m/e 261. Calculated for $C_{13}H_{15}N_3O_3$: C , 59.76; H, 5.79; N, 16.08. Found: C, 59.86; H, 5.79; N, 15.79.

Attempted Preparation of 5-Phenyl-5-[N-(l-ephedrine)]-barbituric Acid

To a solution prepared by dissolving 5.0 g (0.018 mole) of 5-bromo-5-phenylbarbituric acid in 20 ml of methanol was added with constant stirring 5.9 g (0.036 mole) of l-ephedrine with constant stirring. The solution was refluxed for one hour under a condenser equipped with a calcium chloride drying tube. The white precipitate which resulted on cooling was removed by filtration and washed with water. It was then recrystallized from an ethanol-water mixture and dried overnight at 80° under reduced pressure, m.p. 264-265°.

The IR spectrum showed bands at 1675 cm^{-1} (strong, carbonyl) and 1560 cm^{-1} (strong, amine salt). The NMR spectrum (DMSO-d_6) showed absorptions at 9.53 δ (singlet, 2H), 9.10 δ (singlet, 2H), 7.33 δ (singlet, 5H), 7.10 δ (singlet, 5H), 3.23 δ (multiplet, 1H), 2.50 δ (singlet, 3H), and 0.87 δ (doublet, 2H). No molecular ion was observed, but a peak showing possible amine cleavage was observed at m/e 204. Calculated for $C_{20}H_{21}N_3O_4$: C, 65.38, H, 5.76; N, 11.44. Calculated for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.01

H, 6.39; N, 11.36.

5-Phenyl-5-[N-(2-methoxyethylamino)]-barbituric Acid

A solution of 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol was placed in a 100 ml flask equipped with a magnetic stirring bar, a reflux condenser, and a calcium chloride drying tube. To this solution was added 5.4 g (0.072 mole) of 2-methoxyethylamine. The solution warmed on mixing and a small amount of white precipitate formed. The mixture was then refluxed for one hour and the solvent removed on the rotovap. The resinous residue was shaken with water and the white solid which crystallized was filtered, washed with water, and dried. It was then recrystallized from water and dried forty-eight hours in an Abderhalden drying pistol under refluxing acetone, m.p. 76-78°, 9.2 g (94 per cent yield).

The IR spectrum showed bands at 3580 cm^{-1} (medium, NH stretch) and 1700 cm^{-1}(strong, broad, carbonyl). The UV spectrum recorded in 95 per cent ethanol made 0.3 N in NaOH gave two absorptions at λ_{max}226 nm, (ε 21,600) and λ_{max}262 nm, (ε 7,580). The NMR in acetone-d_6 showed bands at 6.83 δ (multiplet, 5H); 2.88 δ (triplet, 2H), 2.68 δ (singlet, 3H), and 2.30 δ (triplet, 2H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.09; H, 5.72; N, 14.99.

5-Phenyl-5-[N-(allylamino)]-barbituric Acid

In 40 ml of methanol contained in a 100 ml round-bottomed flask fitted with a condenser and calcium chloride drying tube were introduced 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid and when

dissolution was effected 4.2 g (0.072 mole) of freshly distilled allylamine was added. The solution was observed to warm on mixing. This mixture was then heated at reflux for one hour and then approximately one-half of the solvent removed on a rotatory evaporator. The solid was removed by filtration and washed with 30 ml of H_2O. The precipitate was then dried after which it was recrystallized from the minimal amount of 95 per cent ethanol and dried again at 80° in vacuo overnight, m.p. 185-186°, 7.6 g (83 per cent yield).

The IR spectrum showed absorptions at 3280 cm^{-1} (broad, medium) 1760 cm^{-1} (strong, carbonyl), and 1700 cm^{-1} (strong, carbonyl). The UV spectrum in 0.3 N NaOH in 95 per cent ethanol showed bands at λ_{max}226 nm, (ϵ 16,700), and λ_{max}264 nm, (ϵ 5,520). The NMR spectrum in DMSO-d_6 showed absorptions at 11.67 δ (singlet, 2H), 7.29 δ (singlet, 5H), 5.00 δ (doublet, 2H), 3.43 δ (multiplet, 1H), 3.04 δ (multiplet, 2H). No molecular ion was observed in the mass spectrum. Calculated for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.09; H, 5.10; N, 16.31.

Attempted Preparation of 5-phenyl-5-[N-(benzimidazole)]-barbituric Acid

Five g (0.018 mole) of 5-bromo-5-phenylbarbituric acid was dissolved in 20 ml of methanol and to this solution was added 4.2 g (0.036 mole) of benzimidazole. The solution was then heated with reflux for one hour and cooled. Ethanolic HCl was then added until precipitation was complete. The solid was then removed by filtration, washed with water, dried and recrystallized from 95 per cent ethanol. A positive halogen test was obtained with $AgNO_3$ and the solid was then

re-dissolved in 30 ml of 0.6 N aqueous sodium hydroxide and extracted with 30 ml of diethyl ether. Precipitation was then effected by addition of 10 per cent (w/w) sulfuric acid and the solid was recrystallized again from 95 per cent ethanol and dried, m.p. 228-229°.

The IR spectrum showed bands at 1742 cm^{-1} (strong, carbonyl) and 1715 cm^{-1} (strong, carbonyl). The NMR spectrum (DMSO-d_6) showed absorptions at 12.17 δ (singlet, 2H), 8.37 δ (singlet, 1H), 7.50 δ (singlet, 5H) and 6.93 δ (multiplet, 3H). The mass spectrum gave a "molecular" ion at m/e 320.102 (calculated, 320.091). Calculated for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49. Found: C, 54.94; H, 3.72; N, 14.83.

5-Phenyl-5-[N-(benzylamino)]-barbituric Acid

10.0 g (0.036) mole of 5-bromo-5-phenylbarbituric acid was dissolved in 40 ml of methanol and then 7.8 g (0.072 mole) freshly distilled benzylamine was added. Heat was observed to be evolved from the reaction vessel. This mixture was then heated to the reflux temperature and refluxing was continued for one hour. A pinkish colored precipitate was visible at this time (more precipitation effected by evaporation) of ca. one-half of the methanol. The solid was then removed, washed with water and dried. It was then recrystallized from an ethanol-water mixture and dried, m.p. 203-204°, 9.3 g (85 per cent yield). An analytical sample was prepared by a second recrystallization in the above mentioned solvent system and drying overnight at 80° at 1 mm.

The IR spectrum showed significant bands at 3490 cm^{-1} (wide, N-H

stretch) and three carbonyl bands at 1760 cm^{-1} (shoulder), 1710 cm^{-1} (shoulder) and 1690 cm^{-1} (strong), respectively. The UV spectrum in 0.3 N NaOH in 95 per cent ethanol showed the usual bands at λ_{max} 226 nm, (ϵ 24,800) and λ_{max} 261 nm, (ϵ 7,790). The NMR spectrum (DMSO-d_6) revealed absorptions at 11.70 δ (singlet, 2H), 7.50 δ (singlet, 5H), 7.40 δ (singlet, 5H), 3.73 δ (barely split singlet, 2H), and 3.23 δ (broad singlet, 1H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 66.18; H, 4.99; N, 13.45.

5-Phenyl-5-[N-(3-amino-1-propanol)]-barbituric Acid

A solution was prepared by dissolving 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol and adding 5.4 g (0.072 mole) of freshly distilled 3-amino-1-propanol. The solution warmed on mixing. Heat was then applied and the mixture was refluxed for one hour and cooled. No precipitate was visible at this time and the solution was refrigerated overnight. Still no precipitate appeared and the solvent was removed on a rotatory evaporator and the residue shaken vigorously with water. The white crystalline solid which formed was removed by filtration and washed with water. Recrystallization was effected from an ethanol-water mixture, m.p. 190-191°, 8.6 g (88 per cent yield). The analytical sample was obtained by recrystallizing twice more from the same solvent system and drying overnight in an Abderhalden drying pistol using refluxing benzene.

The IR spectrum revealed absorptions at 3520 cm^{-1} (strong, OH stretch), 3350 cm^{-1} (strong, N-H stretch), 1730 cm^{-1} (strong, carbonyl)

and 1700 cm^{-1} (strong, carbonyl). The UV spectrum in 95 per cent ethanol 0.3 N in NaOH showed λ_{max} 226 nm, (ϵ 14,300) and λ_{max} 262 nm, (ϵ 4,880). The NMR spectrum in DMSO-d_6 showed absorptions at 7.43 δ (singlet, 5H), 3.50 δ (triplet, 2H), 2.52 δ (multiplet, 2H), and 1.67 δ (multiplet, 2H). The mass spectrum showed the expected molecular ion at m/e 277, (calculated mass = 277). Calculated for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.39; H, 5.51; N, 15.05.

5-Phenyl-5-[N-(l-amphetamino)]-barbituric Acid

Levo-amphetamine (9.8 g, 0.072 mole) ($[a]_o^{25°}$ = - 33.0°, neat) was added to a solution of 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol. On stirring, heat was evolved from the reaction vessel. Heat was then applied and the solution was refluxed for two and one-half hours. The solution was then cooled and ethanolic HCl added. No precipitate formed. The solvent was removed on a rotatory evaporator and the residue was dissolved in an acetone-water mixture. When the pH was adjusted to ca. 7 by the addition of aqueous ammonia a large amount of white precipitate formed. The solid was removed by filtration, washed with water, and dried. Following recrystallization from an ethanol-water mixture, m.p. 181-182°, 11.1 g (93 per cent yield). An analytical sample was prepared by recrystallizing a small amount of the solid from the above solvent system and drying overnight at 80° in vacuo.

The optical rotation of this product in DMSO was $[a]_o^{25°}$ = (-) 7.92°. The IR spectrum showed significant bands at 3250 cm^{-1} (medium, sharp, NH stretch), 1750 cm^{-1} (strong, carbonyl), and 1720 cm^{-1} (strong,

carbonyl). The UV spectrum in 0.3 N NaOH in 95 per cent ethanol showed absorptions at λ_{max} 226 nm, (ϵ 27,900) and λ_{max} 261 nm, (ϵ, 9850). The NMR spectrum (DMSO-d_6) showed absorptions at 10.92 δ (singlet, 2H), 7.47 δ (singlet, 5H), 7.20 δ (singlet, 5H), 2.80 δ (multiplet, 4H), and 0.33 δ (doublet, 3H). The mass spectrum showed benzyl cleavage at the calculated position m/e 247. Calculated for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.65; H, 5.70; N, 12.39.

5-Phenyl-5-[N-(d-amphetamino)]-barbituric Acid

Nine and eight-tenths grams (0.072 mole) of d-amphetamine ($[a]_o^{25°}$ = + 33.0, neat) was introduced into a 100 ml round-bottomed flask equipped with a condenser and a calcium chloride drying tube and containing 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid dissolved in 40 ml of methanol. Heat was evolved on addition of the amine. This mixture was then heated for two and one-half hours at the reflux temperature after which it was cooled. Ethanolic HCl was added in an attempt to induce precipitation. When no precipitate formed, the solvent was removed on the rotatory evaporator and the residue dissolved in a mixture of acetone and water. When the pH was adjusted to ca. 7 by the addition of aqueous ammonia a voluminous quantity of white precipitate formed. This solid was removed by filtration under reduced pressure, washed with water, and dried. Recrystallization was effected from an ethanol-water mixture, m.p. 181-182°, 11.0 g (93 per cent yield). An analytical sample was prepared by recrystallizing a small amount of the solid from the above mentioned solvent pair and drying overnight in an Abderhalden drying pistol under refluxing benzene at 1 mm pressure.

The optical rotation of this compound was found to be $[a]_D^{25°}$ = + 7.48°. The IR spectrum showed absorptions at 3250 cm^{-1} (medium, sharp, N-H stretch), 1750 cm^{-1} (sharp, carbonyl), and 1720 cm^{-1} (sharp, carbonyl). The UV spectrum showed bands at λ_{max}226 nm, (ε, 27,100) and λ_{max}260 nm, (ε, 9,940), when recorded in 95 per cent ethanol made 0.3 N in NaOH. The NMR spectrum (DMSO-d_6) showed absorptions at 10.92 δ (singlet, 2H), 7.47 δ (singlet, 5H), 7.20 δ (singlet, 5H), 2.80 δ (multiplet, 4H), and 0.33 δ (doublet, 3H). The mass spectrum showed benzyl cleavage at the calculated position m/e 247. Calculated for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.50; H, 5.77; N, 12.40.

5-Phenyl-5-[N-(p-phenetidino)]-barbituric Acid

In a 100 ml boiling flask containing a solution prepared from 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol was introduced 9.8 g (0.072 mole) of freshly distilled p-phenetidine. The solution became warm on addition of the amine. This solution was then heated with reflux under a condenser fitted with a and calcium chloride drying tube for one hour and cooled.
The precipitate was removed by filtration through sintered glass under reduced pressure and dried. The precipitate was then boiled in water and dried and the same treatment repeated with acetone. It was insoluble in either of the above. The solid was dissolved in the minimal amount of 0.6 N aqueous sodium hydroxide and extracted with diethyl ether. The free acid was then precipitated from the alkaline layer by addition of 10 per cent sulfuric acid. The pink crystals were

removed by filtration and dried forty-eight hours at 80° under 1 mm pressure, m.p. 246-247°, 7.3 g (61 per cent yield).

The IR spectrum showed absorptions at 3370 cm^{-1} (weak, N-H stretch), 1750 cm^{-1} (medium, carbonyl), and 1700 cm^{-1} (strong, carbonyl). The UV spectrum as determined in 95 per cent ethanol made 0.3 N in NaOH showed absorptions at λ_{max} 226 nm, (ϵ, 27,800), λ_{max} 247 nm, (ϵ, 20,000) and $\lambda_{shoulder}$ 268 nm, (ϵ, 9,090). The NMR spectrum as determined in dimethyl sulfoxide, d_6 showed bands at 11.83 δ (singlet, 2H), and 1.27 δ (triplet, 3H). The mass spectrum showed a peak for the molecular ion at the calculated position, 339. Calculated for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: c, 63.89; H, 5.09; N, 12.26

5-Phenyl-5-[N-(4-benzylpiperidino)]-barbituric Acid

A solution of 5 g (0.018 mole) of 5-bromo-5-phenylbarbituric acid in 20 ml of methanol was introduced into a 100 ml round-bottomed flask fitted with a condenser and a calcium chloride drying tube and 6.3 g (0.036 mole) of 4-benzylpiperidine was added. The solution warmed on mixing. Heat was then applied and the solution was refluxed for one hour. A precipitate is visible even at the reflux temperature. The mixture was then cooled and approximately one-half of the solvent was removed on a rotatory evaporator. The solid was removed by filtration, washed with water, and dried. Recrystallization was achieved from an ethanol-water mixture and an analytical sample was dried at 80° in vacuo for a period of forty-eight hours, m.p. 243-244°, 5.8 g (86 per cent yield).

The IR spectrum showed the typical carbonyl absorption at 1690 cm^{-1} (strong). The UV spectrum measured in 0.3 N NaOH in 95 per cent ethanol showed the familiar peaks at λ_{max} 226 nm, (ε, 22500) and λ_{max} 264 nm, (ε 6,730). The NMR spectrum (DMSO-d_6) showed absorptions at 11.77 δ (singlet, 2H), 7.54 δ (singlet, 5H), 7.31 δ (singlet, 5H), 2.37 δ (broad, multiplet, 7H) and 1.45 δ (broad, multiplet, 4H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{22}H_{23}N_3O_3$: C, 70.00; H, 6.14; N, 11.13. Found: C, 70.01; H, 6.18; N, 11.08.

Attempted Preparation of 5-Phenyl-5-[N-(2,2,6,6-tetramethylpiperidino)]-barbituric Acid

Ten and two tenths grams (0.072 mole) of freshly distilled 2,2,6,6-tetramethylpiperidine was introduced into a 100 ml flask containing 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol. Heat was evolved on mixing and a dense white precipitate settled almost immediately. Stirring was continued at room temperature for 30 minutes and the solid was then removed by filtration, washed with copious quantities of water, and dried. This solid product was then recrystallized from the minimal amount of 95 per cent ethanol twice without changing the melting point. An analytical sample was then dried in an Abderhalden drying pistol utilizing refluxing toluene at 1 mm pressure. This compound gave a positive Beilstein test, m.p. 251-252° (dec), 10.8 g (72 per cent yield).

The IR spectrum showed two carbonyl absorptions at 1720 cm^{-1} (strong) and 1670 cm^{-1} (strong) and a band attributed to N-H bending at 1620 cm^{-1} (strong). The UV spectrum in 0.3 N NaOH in 95 per cent

ethanol showed bands at λ_{max}227 nm, (ε 13,700) and λ_{max}269, (ε 7,030). The NMR (trifluoracetic acid) showed absorptions at 7.05 δ (singlet, 5H), 1.32 δ (singlet, 6H), and 1.03 δ (singlet, 12H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{19}H_{26}N_3O_3Br$: C, 53.78; H, 6.18; N, 9.90; Br, 18.83. Found: C, 53.99; H, 6.23; N, 10.01; Br, 18.73.

5-[Phenyl-5-[N-(morpholino)]-barbituric Acid

Morpholine (6.2 g, 0.072 mole) was introduced into a solution of 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol contained in a 100 ml round-bottomed flask equipped with a reflux condenser and a calcium chloride drying tube. The mixture was then heated with reflux for one hour and cooled to room temperature. A dense white precipitate settled on cooling and ca. one-half of the solvent was removed on a rotatory evaporator in an attempt to induce further precipitation. The solid was then removed by filtration, washed with water and dried. A suitable solvent for recrystallization was not found. However, by boiling the solid with 250 ml of water, filtering while hot, and drying gave a solid which when dried at 80° under 1 mm of pressure overnight analyzed for the expected product, m.p. 263-264°, 9.2 g (90 per cent yield).

The IR spectrum revealed a band at 1710 cm^{-1} (broad, strong). The UV spectra in 0.3 N NaOH in 95 per cent ethanol showed absorptions at λ_{max}225 nm, (ε, 20.900) and λ_{max}265 nm, (ε, 6,360). The NMR spectrum recorded in DMSO-d_6 showed absorptions at 11.67 δ (singlet, 2H), 7.50 δ (singlet, 5H), 3.60 δ (broad multiplet, 4H), and 2.63 δ (broad

multiplet, 4H). The mass spectrum showed m/e at 289 (calculated mass = 289). Calculated for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.52. Found: C, 58.26; H, 5.41; N, 14.41.

5-Phenyl-5-[N-(N'-methylpiperazino)]-barbituric Acid

In 40 ml of methanol containing 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid contained in a boiling flask was introduced with constant stirring 7.2 g (0.072 mole) of N-methylpiperazine. The solution was then brought to the reflux temperature and refluxing was continued for one hour. When no precipitate was visible on cooling, the solvent was removed with the aid of a rotatory evaporator. A solid was crystallized following vigorous shaking with water and this was filtered through a sintered-glass funnel under reduced pressure, washed with water and dried. Following recrystallization from 95 per cent ethanol, m.p. 245-246°, 7.1 g (71 per cent). An analytical sample was prepared by a second recrystallization from the same solvent and drying at 80° overnight under reduced pressure (no melting point change).

The IR spectrum showed significant absorptions at 1690 cm^{-1} (strong, carbonyl) and 1590 cm^{-1} (broad, N-H band). The UV spectrum in 95 per cent ethanol made 0.3 N in NaOH showed the usual bands at λ_{max}226 nm, (ε, 15,200) and λ_{max}265 (ε, 5,180). The NMR spectrum in DMSO-d_6 showed absorptions at 8.50 δ (broad singlet, 2H), 7.42 δ (singlet, 5H), 2.58 δ (broad singlet, 4H), 2.35 δ (broad singlet, 4H) and 2.13 δ (singlet, 3H). The mass spectrum showed a molecular ion at the calculated position, m/e 302. Calculated for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.37; H, 6.04; N, 18.40.

Attempted Preparation of 5-Phenyl-5-[N-(anilino)]-barbituric Acid

Five grams (0.018 mole) of 5-bromo-5-phenylbarbituric acid was dissolved in 20 ml of methanol and to this solution was added with constant stirring 3.3 g (0.036 mole) of freshly distilled aniline. The solution yellowed and a precipitate formed almost immediately. The solution was stirred for one hour, filtered and washed with water. The precipitate was then dissolved in 30 ml of 0.6 N aqueous NaOH and extracted with an equal portion of diethyl ether. The alkaline layer was then acidified with 10 per cent (w/w) sulfuric acid and the solid removed by filtration. After recrystallization from 95 per cent ethanol and drying overnight at 110° in vacuo, the solid melted at 260-261°.

The IR spectrum showed bands at 1685 cm^{-1} (strong, carbonyl) and 1500 cm^{-1} (medium NH bending). The NMR (DMSO-d_6) showed two absorptions one at 11.22 δ (singlet, 2H) and 7.30 δ (singlet, 5H). The mass spectrum showed a large peak at 204. Calculated for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Calculated for $C_{10}H_8N_2O_3$: C, 58.32; H, 3.95; N, 13.72. Found: C, 58.74; H, 4.04; N, 13.82.

5-Phenyl-5-[N-(N'-β-hydroxyethylpiperazino)]-barbituric Acid

Eight and four-tenths grams (0.072 mole) of N-β-hydroxyethylpiperazine was introduced into a flask containing a solution prepared by dissolving 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol. Some evolution of heat was observed on mixing. The mixture was then heated with reflux for one hour and cooled. When no precipitate was visible, the solvent was removed on the rotovap to give a slightly orange resin. A while crystalline substance formed on prolonged shaking with distilled water. The solid was removed by filtra-

tion, washed with water, and dried. This substance was then recrystallized from an ethanol-water mixture. An analytical sample was prepared by recrystallizing a second time from ethanol-water and drying in an Abderhalden drying pistol utilizing benzene at the reflux temperature and one mm pressure, m.p. 246-246.5°, 7.8 g (67 per cent yield).

The IR spectrum showed significant bands at 3500 cm^{-1} (broad, OH stretch), 1700 cm^{-1} (strong, carbonyl), and 1600 cm^{-1} (strong, NH bend). The UV spectrum in 95 per cent ethanol made 0.3 N in NaOH showed the usual two bands at λ_{max} 226 nm, (ϵ, 21,900) and λ_{max} 264 nm, (ϵ, 6,450). The NMR spectrum (DMSO-d_6) showed bands at 8.00 δ (broad singlet, 2H), 7.43 δ (singlet, 5H), 3.50 δ (triplet, 2H), and 2.48 % (broad multiplet, 10H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.59; H, 6.18; N, 17.08.

Attempted Preparation of 5-phenyl-5-[N-(1-α-methylbenzylamino)]-barbituric Acid

A solution was prepared by dissolving 5.0 g (0.018 mole) of 5-bromo-5-phenylbarbituric acid in 20 ml of methanol and adding 4.4 g (0.036 mole) of l-(-)α-methylbenzylamine. Some heating of the reaction vessel was observed on mixing. This mixture was then refluxed for thirty minutes and cooled to room temperature. When no precipitate was visible, the solution was evaporated to near dryness on the rotovap to give a yellow resin from which a white solid crystallized on prolonged shaking with an acetone-water mixture. This solid was removed by filtration and recrystallized from a methanol-water mixture and dried

overnight at 80° under reduced pressure to give a white crystalline solid, m.p. 246-247°.

The IR spectrum showed absorptions at 1690 cm^{-1} (strong, carbonyl) and 1570 cm^{-1} (string, attributed to an amine salt). The NMR spectrum (DMSO-d_6) showed bands at 9.38 δ (singlet, 2H), 7.18 δ (singlet, 5H), 7.00 δ (singlet, 5H), 1.92 δ (multiplet, 1H), and 1.22 δ (doublet, 3H). No molecular ion was observed. Calculated for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Calculated for $C_{18}H_{19}N_3O_3$: C, 66.45; N, 12.91. Found: C, 66.03; H, 5.89; N, 12.88.

5-Phenyl-5-[N-(1,2,3,6-tetrahydropyridino)]-barbituric Acid

A solution of 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol was first prepared. To this was now added 6.0 g (0.072 mole) of 1,2,3,6-tetrahydropyridine (freshly distilled) with stirring. The solution takes on a bromine color on addition of the amine and heat is evolved. Heat was now applied and the mixture was allowed to reflux for one hour under a calcium chloride drying tube. Approximately one-half of the solvent was removed on a rotatory evaporator and water was added to the mixture. A red-orange resin forms on addition of water from which, on prolonged stirring, a fluffy-white precipitate separated and was removed by filtrtion, washed with water, and dried. A suitable solvent was not found for recrystallization. However, by boiling in water, filtering while hot, and drying gave a white solid, m.p. 192-193°, 8.4 g (83 per cent yield). The analytical sample was dried overnight at 110° under one mm pressure.

The IR spectrum showed significant bands at 1760 cm^{-1} (shoulder,

carbonyl) and 1690 cm^{-1} (strong, carbonyl). The UV spectrum recorded in 0.3 N NaOH in 95 per cent ethanol gave bands at λ_{max}226 nm, (ε, 23,900) and λ_{max}264 nm, (ε, 7,610). The NMR spectrum in DMSO-d_6 showed absorptions at 11.68 δ (singlet, 2H), 7.47 δ (singlet, 5H), 5.38 δ (multiplet, 2H), 3.15 δ (broad multiplet, 2H), 2.70 δ (broad multiplet, 2H) and 2.07 δ (broad multiplet, 2H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{15}H_{15}N_3O_3$: C, 63.15, H, 5.30; N, 14.73. Found: C, 63.07; H, 5.33; N, 14.57.

5-Phenyl-5-[N-(1,2,3,4-tetrahydroisoquinolino)-barbituric Acid

In a 100 ml round-bottom flask containing a solution prepared from 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol was introduced 9.6 g (0.072 mole) of freshly distilled, 1,2,3,4-tetrahydroisoquinoline. Some initial heating was observed on addition of the amine, but no precipitate formed. The mixture was then refluxed for one hour and the solvent removed on the rotatory evaporator. A white solid could be crystallized from the residual resin after vigorous shaking with water, and this was removed by filtration, washed with water, and dried. Recrystallization was effected from an ethanol-water mixture and the analytical sample dried overnight at 80° under vacuum, m.p. 236-237° (dec), 6.4 g (54 per cent yield).

The IR spectrum showed absorptions at 1730 cm^{-1} (strong, carbonyl) and 1690 cm^{-1} (strong, carbonyl). The UV spectrum in 95 per cent ethanol made 0.3 N in sodium hydroxide showed absorptions at λ_{max}225 nm, (E, 27,100) and λ_{max}265 nm, (ε, 8,030). The NMR spectrum in DMSO-d_6 showed bands at 11.73 δ (singlet, 2H), 7.50 δ (singlet, 5H), 7.13 δ (broad

multiplet, 4H), 3.83 δ (doublet, 2H), and 1.15 δ (broad multiplet, 4H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.13; H, 5.18; N, 12.41.

5-Phenyl-5-[N-(ethyl-N'-piperazinocarboxylato)]-barbituric Acid

Ten grams (0.036 mole) of 5-bromo-5-phenylbarbituric acid was dissolved in 40 ml of methanol. Following dissolution, 11.4 g (0.072 mole) of ethyl N-piperazinocarboxylate was added while stirring was continued. This mixture was then boiled with reflux for one hour, cooled, and when no precipitate was visible, the solvent was removed on a rotatory evaporator. A white crystalline solid was induced to form on vigorous shaking with water and this was removed by filtration and washed with water. Following drying it was recrystallized from an ethanol-water mixture and dried, m.p. 211-212°, 11.4 g (90 per cent yield). An analytical sample was prepared by a second recrystallization from the same solvent system and drying in an Abderhalden drying pistol utilizing refluxing toluene (no change in m.p.).

The IR showed absorptions at 1740 cm^{-1} (shoulder, carbonyl), 1700 cm^{-1} (strong, carbonyl), and 1660 cm^{-1} (shoulder, carbonyl). The UV spectrum in 0.3 N NaOH in 95 per cent ethanol showed bands at λ_{max} 226 nm, (ε, 20,500) and λ_{max} 264 nm (ε6,880). The NMR spectrum (DMSO-d_6) showed bands at 11.50 δ (singlet, 2H), 7.33 δ (singlet, 5H), 3.90 δ (quartet, 2H), 3.23 δ (broad multiplet, 8H), and 1.07 δ (triplet, 3H). The mass spectrum gives a molecular ion at 360 (calculated = 360). Calculated for $C_{17}H_{20}N_4O_5$: C, 56.70; H, 5.55; N, 15.55. Found: C,

56.49; H, 5.57; N, 15.36.

Salt of 5-Phenyl-5-[N-(2-aminopyrimidino)]-barbituric Acid

To a solution prepared by dissolving 10.0 g of 5-bromo-5-phenyl-barbituric acid in 40 ml of methanol was added with constant stirring 6.8 g (0.036 mole) of 2-amino-pyrimidine. A dense white precipitate settled almost immediately and stirring under a reflux condenser fitted with a calcium chloride drying tube was continued for one hour. At this time the solid was removed by filtration, washed with copious amounts of water, and dried. The precipitate was then recrystallized from an ethanol-water mixture and dried at 80° under reduced pressure. This compound gave a positive Beilstein test, m.p. 169-179°, 10.9 g (81 per cent yield).

The IR spectrum showed absorptions at 3400 cm^{-1} (strong, N-H stretch), 1730 cm^{-1} (strong, carbonyl), 1690 cm^{-1} (strong, carbonyl), and 1625 cm^{-1} (sharp C = N-stretch). The UV spectrum as recorded in 0.3 N NaOH in 95 per cent ethanol showed bands at λ_{max} 227 nm, (ϵ, 27,200) and λ_{max} 278 nm, (ϵ, 6,700). The NMR spectrum (DMSO-d_6) showed bands at 11.63 δ (singlet, 2H), 8.33 δ (doublet, 2H), 7.45 δ (singlet, 5H), and 6.67 δ (triplet, 1H). No molecular ion was observed. Calculated for $C_{14}H_{12}N_5O_3Br$: C, 44.46; H, 3.20; N, 18.52; Br, 21.02.

5-Phenyl-5-[N-(N'-3-(aminopropyl)-2-pyrrolidinono)]-barbituric Acid

Ten and two tenths grams (0.072 mole) of n-3-(aminopropyl)-2-pyrrolidinone was introduced into a solution prepared by dissolving 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid in 40 ml of methanol. Heat was evolved on mixing and the mixture was then heated

with reflux for one hour in a 100 ml boiling flask equipped with a reflux condenser and a calcium chloride drying tube. At this time a large amount of white precipitate was visible. Approximately one-half of the solvent was then removed on the rotatory evaporator and the solid was removed by filtration, washed with water, and dried. Recrystallization was from 95 per cent ethanol, m.p. 237-238°, 10.2 g (84 per cent yield). The analytical sample was prepared by recrystallizing a second time from the same solvent and drying for seventy-two hours at 110° and 1 mm pressure (no m.p. change).

Significant IR bands were found at 3320 cm^{-1} (weak, N-H stretch), 1740 cm^{-1} (strong, carbonyl), 1700 cm^{-1} (strong, carbonyl), and 1630 cm^{-1} (strong, N-H bend). The UV spectrum as determined in 95 per cent ethanol made 0.3 N in NaOH showed the usual two bands at λ_{max}225 nm, (ϵ, 20,200), and λ_{max}262 nm, (ϵ 6,180). The NMR spectrum in DMSO-d_6 showed absorptions at 11.53 δ (singlet, 2H), 7.32 δ (singlet, 5H), 3.17 δ (triplet 2H), 3.07 δ (triplet, 2H), 2.37 δ (multiplet, 2H), 1.92 δ (triplet 7H), ~1.78 δ (multiplet, 2H), and 1.47 δ (multiplet, 2H). The mass spectrum did not reveal a molecular ion. Calculated for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.22; H, 5.92; N, 16.15.

5-Phenyl-5[N-(4-aminoantipyreno)]-barbituric Acid

In 60 ml of methanol containing 10.0 g (0.036 mole) of 5-bromo-5-phenylbarbituric acid was dissolved with constant stirring 14.6 g (0.072 mole) of 4-aminoantipyrene. A deep violet colored formed on addition of the amine and heat was evolved. Stirring was continued for one hour under a reflux condenser fitted with a calcium chloride drying

tube. The large volume of dark-colored solid was removed by filtration through sintered glass under reduced pressure. The solid was then recrystallized from 95 per cent ethanol and decolorized by addition of decolorizing charcoal and filtering thoough a one cm Celite base supported in a sintered glass funnel. A second similar treatment and drying for seventy-two hours in an Abderhalden drying pistol utilizing refluxing toluene and one mm pressure gave a finely divided white solid, m.p. 228-229 (dec.), 8.9 g (62 per cent yield).

Significant IR absorptions were observed at 1730 cm^{-1} (strong, carbonyl), 1720 cm^{-1} (strong, carbonyl), and 1680 cm^{-1} (strong, carbonyl). The UV spectrum in 95 per cent ethanol made 0.3 N in sodium hydroxide showed bands at λ_{max}226 nm (ϵ, 22,600) and λ_{max}256 nm (ϵ, 12,800). The NMR spectrum in DMSO-d_6 showed absorptions at 10.96 δ (singlet, 2H), 7.37 δ (singlet, 5H), 7.27 δ (singlet, 5H), 5.13 δ (singlet, 1H), 2.67 δ (singlet, 3H), and 2.03 δ (singlet, 3H). No molecular ion was observed. Calculated for $C_{21}H_{19}N_5O_4$: C, 62.22; H, 4.72; N, 17.27. Found: C, 62.14; H, 4.87; N, 17.14.

Infrared Spectra

The infrared spectra of solid compounds were determined in potassium bromide pellets and recorded using a Perkin-Elmer Model 700 double beam infrared spectrophotometer measuring and recording per cent transmittance versus frequency. The pellets were prepared by adding 1.5 mg of the solid 150 mg of dry potassium bromide. The mixture was intimately mixed by grinding in an agate mortar and compressed into a one-quarter inch diamater disc in a briqueting process. The spectra of

liquid samples were recorded using thin films of the liquids between sodium chloride plates. The sharp polystyrene absorption band at 6.24 microns was used as a reference point for all spectra. The infrared spectra of new compounds prepared in this investigation are reproduced in Appendix A.

Nuclear Magnetic Resonance Spectra

All nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60D analytical spectrometer. The spectra of solid compounds were obtained by dissolving them in deuterated dimethyl sulfoxide, deuterated acetone, or trifluoracetic acid. The use of tetramethylsilane was employed as an internal standard and its single absorption frequency arbitrarily assigned a value of zero as a reference point in calibrating the spectra of the samples.

Ultraviolet Spectra

The ultraviolet spectra of all compounds were recorded on a Cary Model 14 double beam recording spectrophotometer using a deuterium source lamp. A solution of 95 per cent ethanol made 0.3 N in sodium hydroxide was used as the solvent in all cases while the concentration of the substrate ranged from 3.3×10^{-5} M to 5.0×10^{-5} M. Initial spectral readings were made within thirty minutes after mixing. The second readings were made after the solution had been allowed to stand for a period of two hours in a constant temperature bath maintained at 60° and then allowed to cool to room temperature. The spectra of these samples was determined a third time after a period of 24 hours had elapsed. All recordings were versus a cell containing a sample of

solvent.

Optical Rotations

The optical rotation study was done on a Bendix Ericsson-NPL Model 968 automatic polarimeter using a sodium D line filter. The instrument was previously standardized with a sucrose solution and the stated sensitivity is 0.0001° of arc. The Model 968 is in all electronic device and utilizes an electronically controlled, self-balancing, photo-electric polarimeter which employs the Faraday Electro-optic effect.

Mass Spectra

The mass spectral data was obtained on either a Varian Model M-66 double focusing cycloidal mass spectrometer or a Hitachi Perkin-Elmer RMV-7L high resolution mass spectrometer of the Neir-Johnson geometry (tested resolution, 30,000). Standard conditions for samples on the Varian were 70 electron volts and 20 microamps and on the Hitachi were 80 electron volts and 30 microamps. These spectra were recorded by either Mr. George Turner or Mr. Larry Abbey of this institution.

CHAPTER IV

CONCLUSIONS

The method of Gebauer, which had formerly found only limited application, has now been extended, with modifications, to prepare twenty-nine new barbituric acid derivatives. In most cases the work-up has been simplified from that of Gebauer with little or no sacrifice in yield. The similarity of these compounds to known physiologically active compounds augments interest in these molecules, some of which incorporate an amine of known activity into the barbituric acid moiety.

A complete set of spectral data has been recorded for the new barbituric acids. Although the infrared data has not proven useful in establishing that a desired reaction had taken place, it often suggested the formation of an undesired product.

The ultraviolet spectra as recorded in dilute alcoholic sodium hydroxide shown the rationalizable spectra for 5,5-disubstituted barbituric acids when amido-imidol tautomerism involving only the hydrogen in the one-position produces a hydroxyl group in the two-position. All of the new barbituric acids show a band of the same λ_{max} after heating for two hours in solvent (with reduced extinction coefficient in most cases).

The nuclear magnetic resonance spectra revealed the imide hydrogens far downfield, between 8.00 δ and 11.83 δ(in agreement with other barbituric acids). No evidence for tautomerism could be deduced from the

nuclear magnetic resonance spectra as recorded in dimethyl sulfoxide-d_6. However, a possible case of tautomerism in a substituted 2-aminopyrimidine may have been observed. The latter needs additional confirmation.

The salt of 5-phenyl-5-[N-(2,2,6,6-tetramethylpiperidino)]-barbituric acid apparently has a different type of bonding than in each of the other compounds being reported. This is to say that the C_5-carbon is probably not bonded to the nitrogen of the amine as it is in other cases. Data is inconclusive as to exactly what type bonding does exist.

The mass spectra of these compounds showed several characteristic splitting patterns. Some of the most significant peaks were found at m/e 104 and m/e 103 in the phenyl derivatives and m/e 56 and m/e 55 in the ethyl derivatives. These peaks are strongly indicative of a covalent bond between the amine and the barbituric acid moiety in the compounds prepared since these peaks quite probably result from C_6H_5-C-N and C_2H_5-C-N, respectively. The most frequently observed cleavage resulted from McLafferty type rearrangements involving hydrogen transfer from the amine to the carbonyl oxygen at either C_4 or C_6. In the ethyl case two McLafferty rearrangements of this type are possible in theory and both were observed to occur. Many of the new barbituric acids gave molecular ions and nearly all of the ethyl compounds gave either M+ or M-1 ions.

CHAPTER V

RECOMMENDATIONS

By application of a simple synthetic technique and work-up developed during this investigation, a synthetic route to many additional barbiturates is now available. If any of the barbiturates produced prove to be of pharmacological value, other nitrogen systems should be studied. Of particular interest would be amine heterocycles, particularly those containing O or S as the heteroatom.

As a result of this work a number of barbituric acids with electronegative groups in the 5-position are available for kinetics studies on hydrolysis rates to see if a broad correlation does exist between the Newman Rule of Six and hydrolytic reactivity. Detailed studies also need to be done on the spectral changes which these compounds undergo in basic media.

Further investigations need to be made into the nature of the pyrimidine ring in 5-phenyl-5-[N-(2-aminopyrimidino)]-barbituric acid to determine exactly what is causing the two ring nitrogens to become non-equivalent and what role the basicity of the different nitrogen atoms plays. If tautomerism does occur in the free barbituric acid, a rationalization would have to be developed as to why this is not observed in the case of the parent 2-aminopyrimidine (assuming, of course, the work of Gronowitz[50] is correct).

The case of the salt of 5-phenyl-5-[N-(2,2,6,6-tetramethyl-

piperidino)]-barbituric acid needs to be resolved to determine the exact nature of the bonding. A probable first step would be an attempt to remove the HBr to give the free acid.

Closer scrutiny needs to be given the mass spectra of each of these compounds under more closely controlled conditions to make as complete a correlation as possible between the spectra observed for the several compounds. The high sensitivity of mass spectrometers coupled with modern methods for separation needs further investigation as a possible tool in forensic analysis.

It would be of great interest to obtain data regarding the physiological activities of the new potential therapeutic agents which were successfully synthesized during this investigation.

APPENDIX A

INFRARED SPECTRA

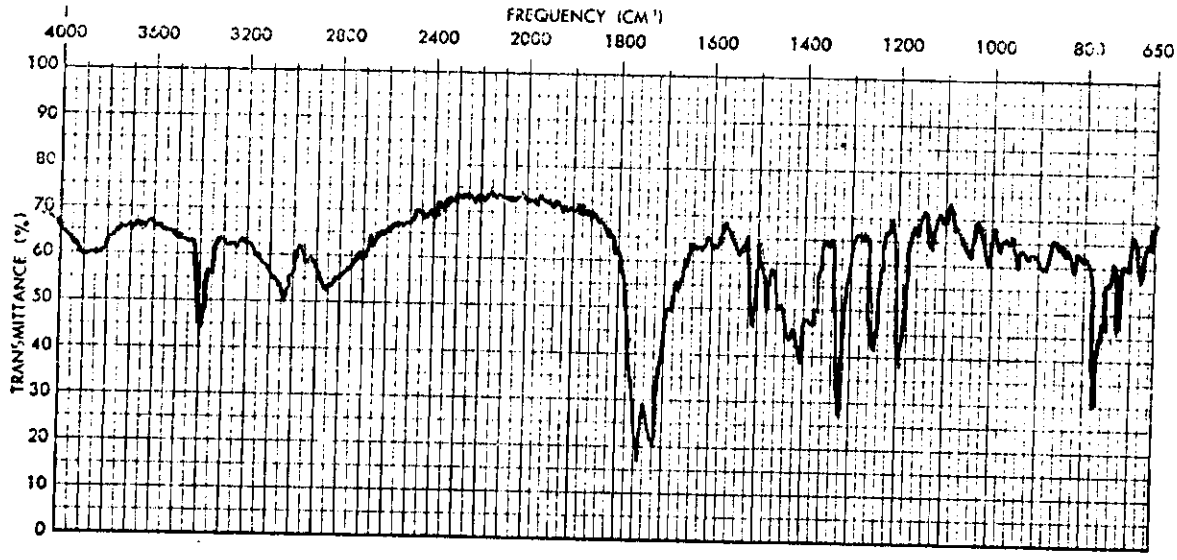


Figure 30. Infrared Spectrum of 5-Ethyl-5-[N-(bemzylamino)]-barbituric Acid

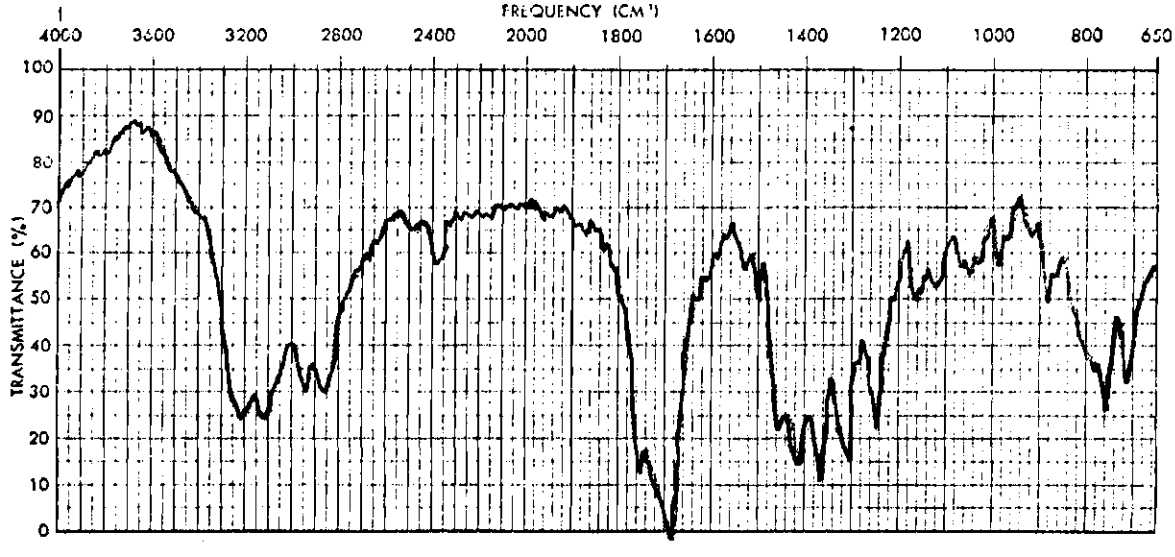


Figure 31. Infrared Spectrum of 5-Ethyl-5-[N-(4-benzylpiperidino)]-barbituric Acid

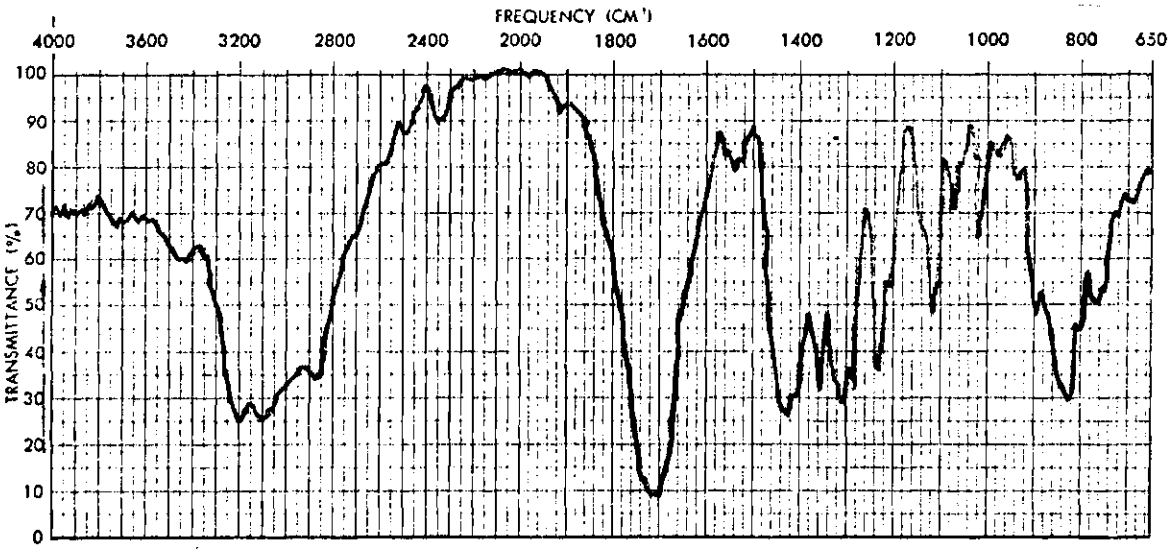


Figure 32. Infrared Spectrum of 5-Ethyl-5-[N-(morpholino)]-barbituric Acid

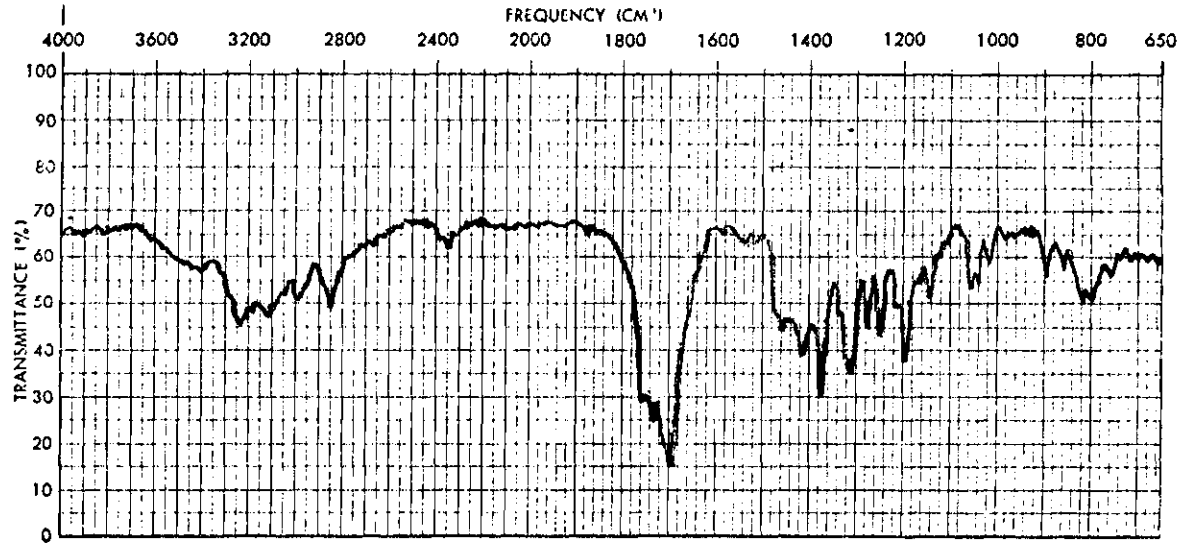


Figure 33. Infrared Spectrum of 5-Ethyl-5-[N-(ethylisonipecotato)]-barbituric Acid

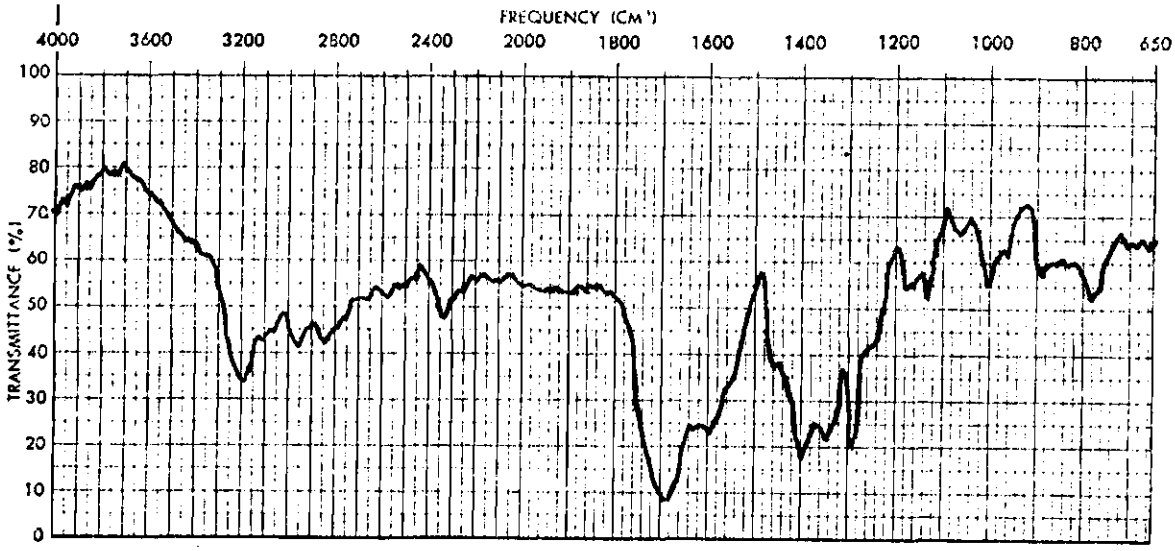


Figure 34. Infrared Spectrum of 5-Ethyl-5[N-(4-methylpiperazino)]-barbituric Acid

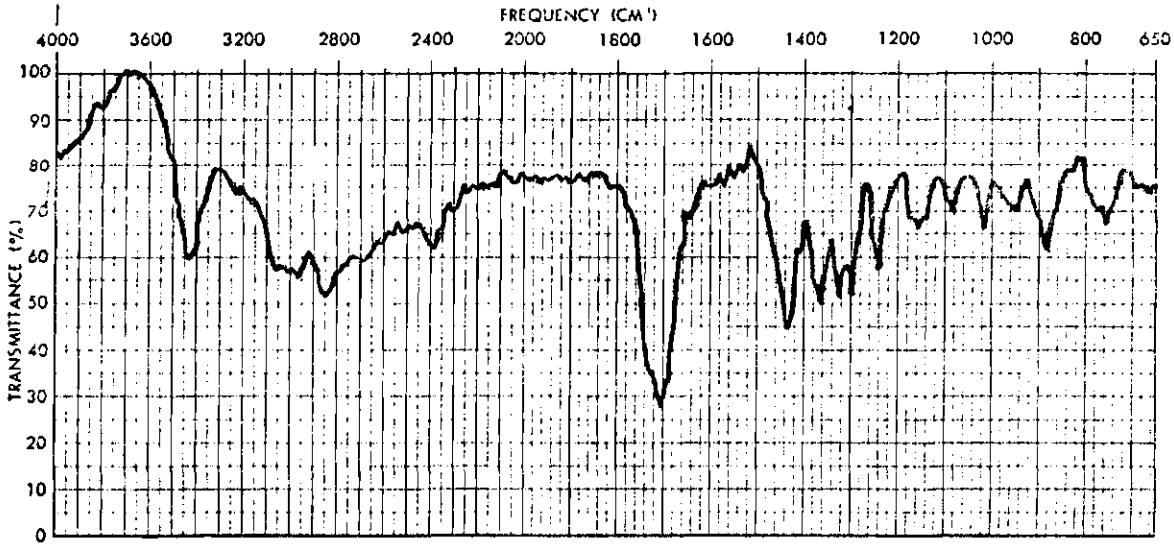


Figure 35. Infrared Spectrum of 5-Ethyl-5-[N-(4-β-hydroxymethyl-piperazino)]-barbituric Acid

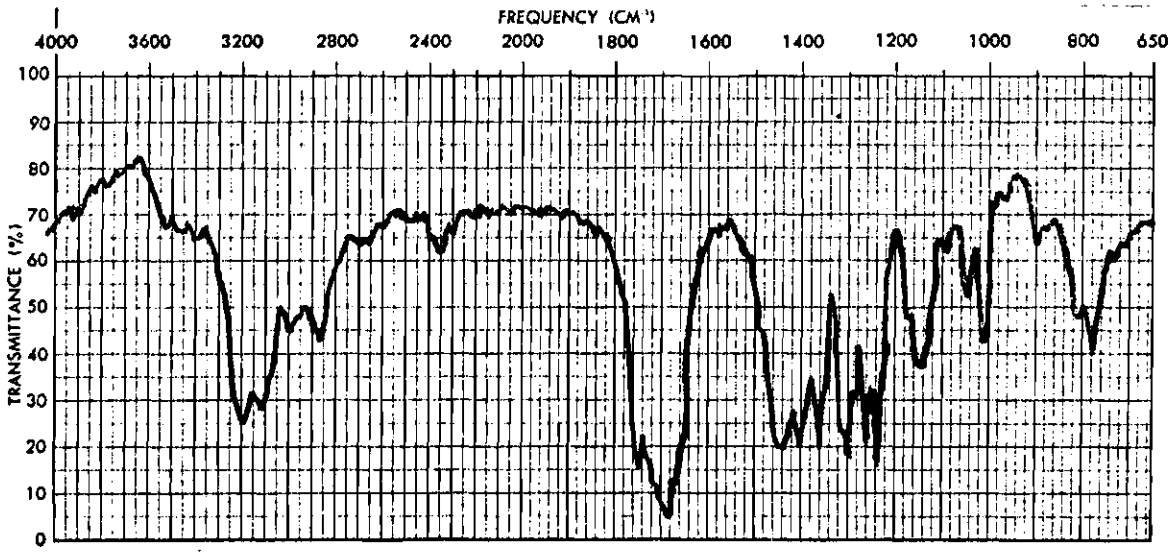


Figure 36. Infrared Spectrum of 5-Ethyl-5-[N-(Ethyl-N'-piperazino-carboxylato)]-barbituric Acid

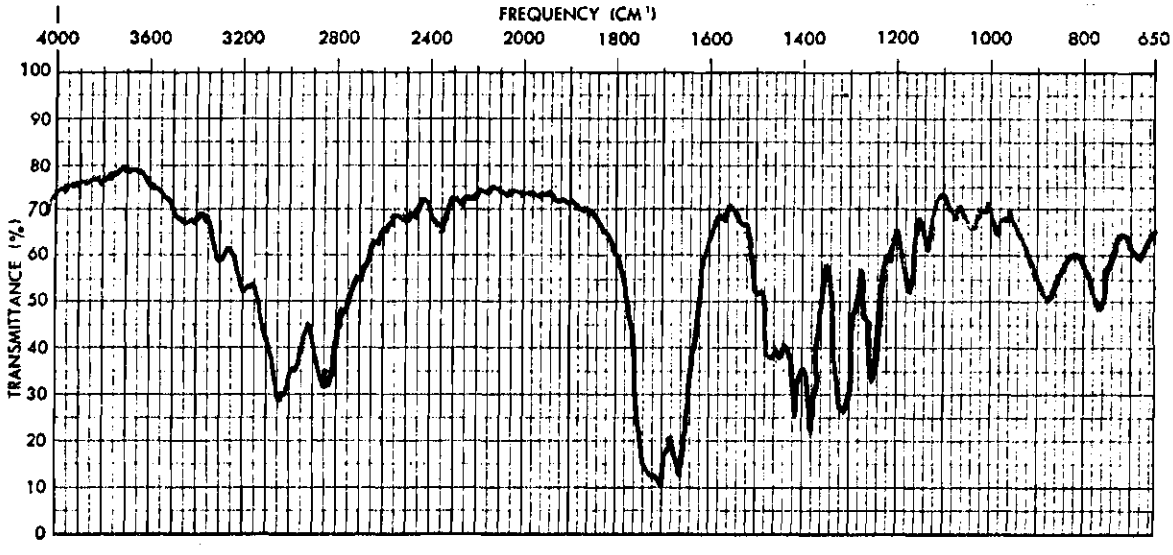


Figure 37. Infrared Spectrum of 5-Ethyl-5-[N-(N'-3-aminopropyl)]-barbituric Acid

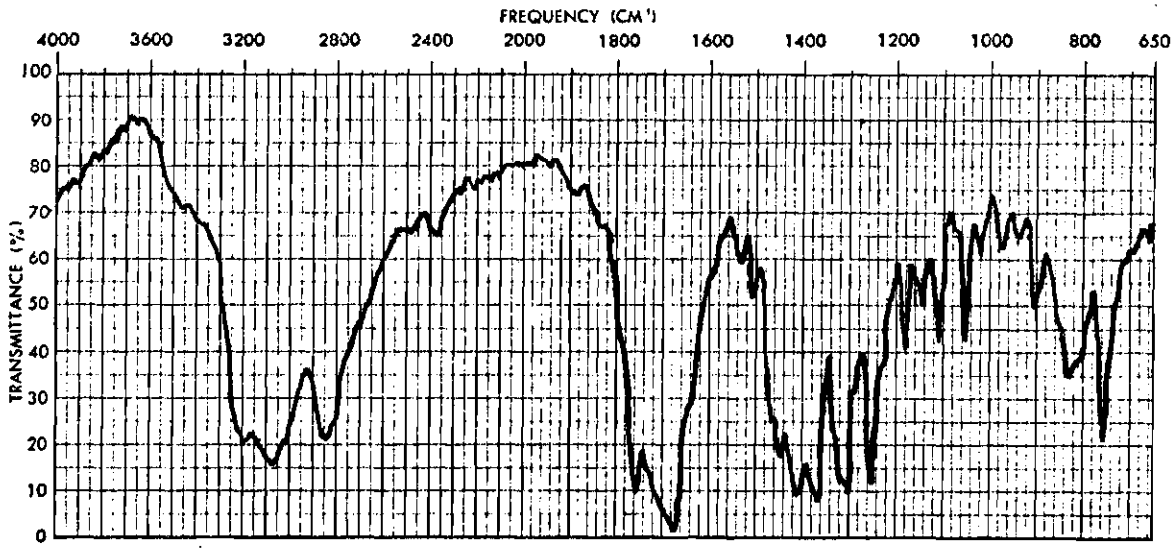


Figure 38. Infrared Spectrum of 5-Ethyl-5-[N-(1.2.3.4-tetrahydroisoquinolino)]-barbituric Acid

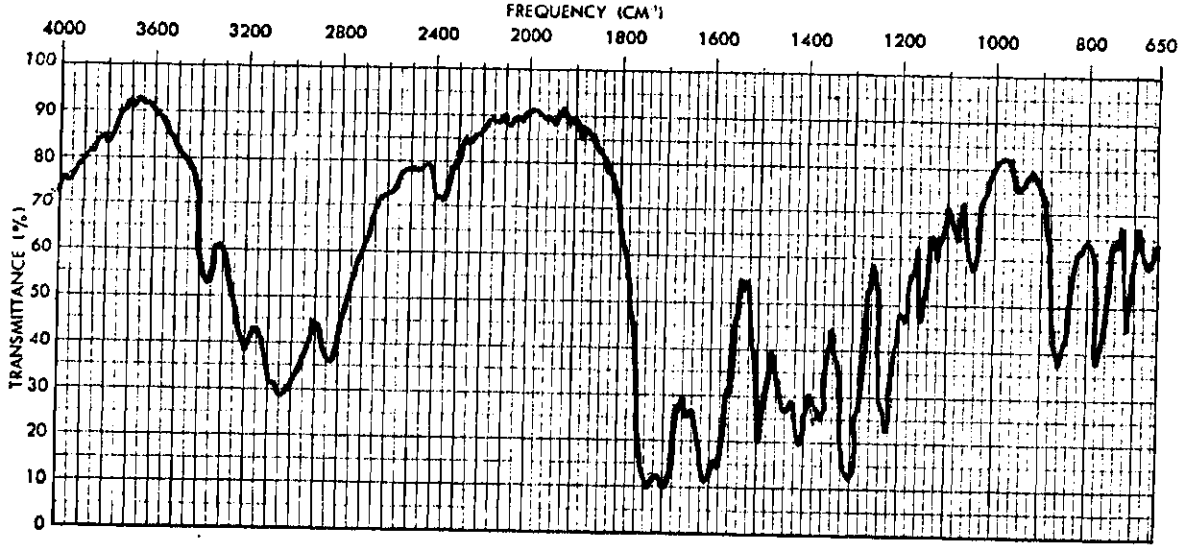


Figure 39. Infrared Spectrum of 5-Ethyl-5-[N-(4-aminoantipyreno)]-barbituric Acid

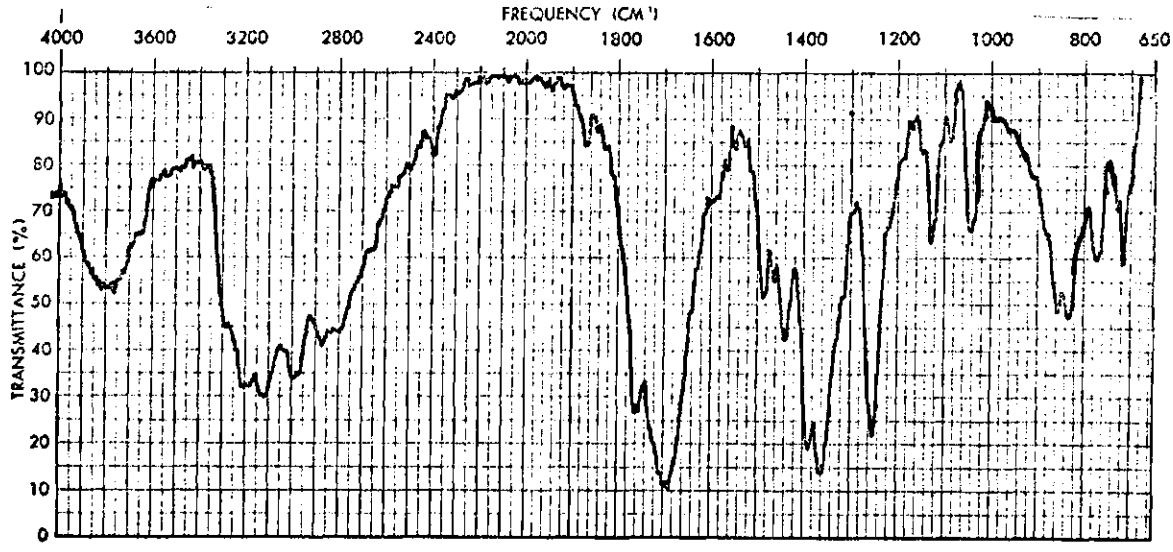


Figure 40. Infrared Spectrum of 5-Phenyl-5-[N-(n-propylamino)]-barbituric Acid

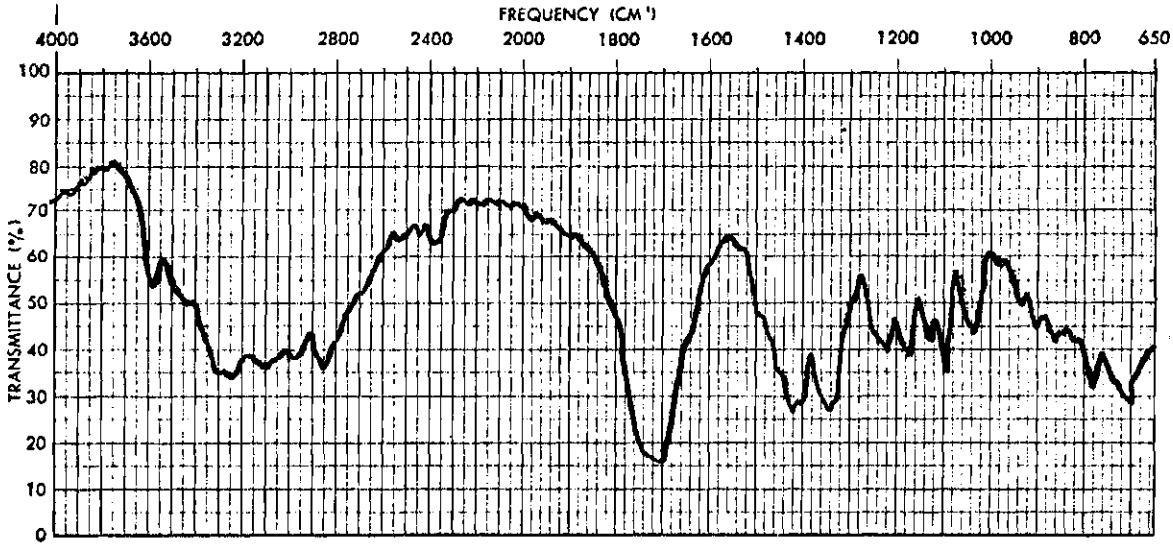


Figure 41. Infrared Spectrum of 5-Phenyl-[N-(2-methoxyethylamino)]-barbituric Acid

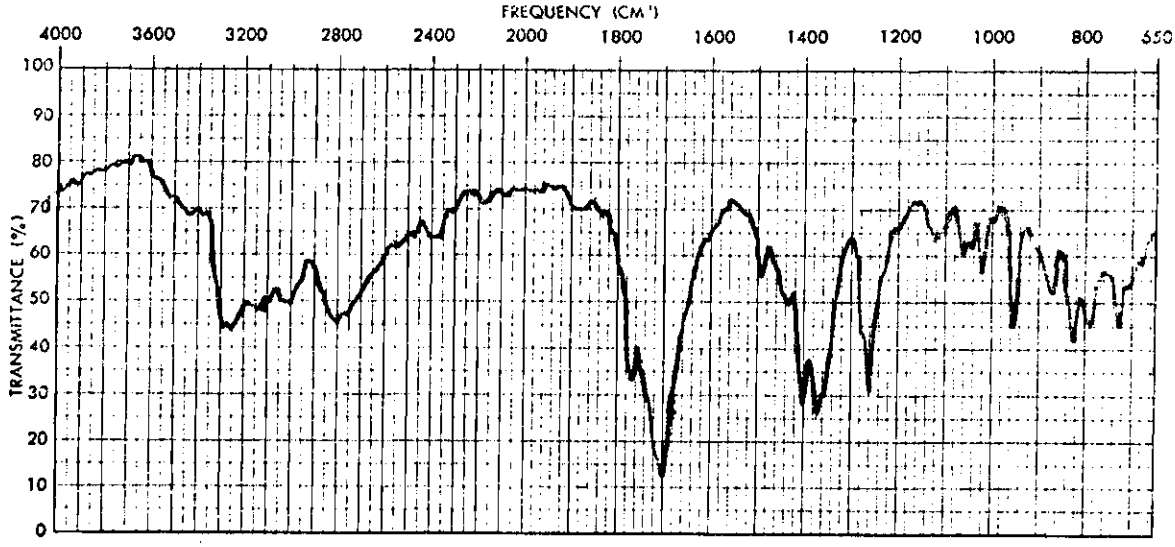


Figure 42. Infrared Spectrum of 5-[N-(allylamine)]-barbituric Acid

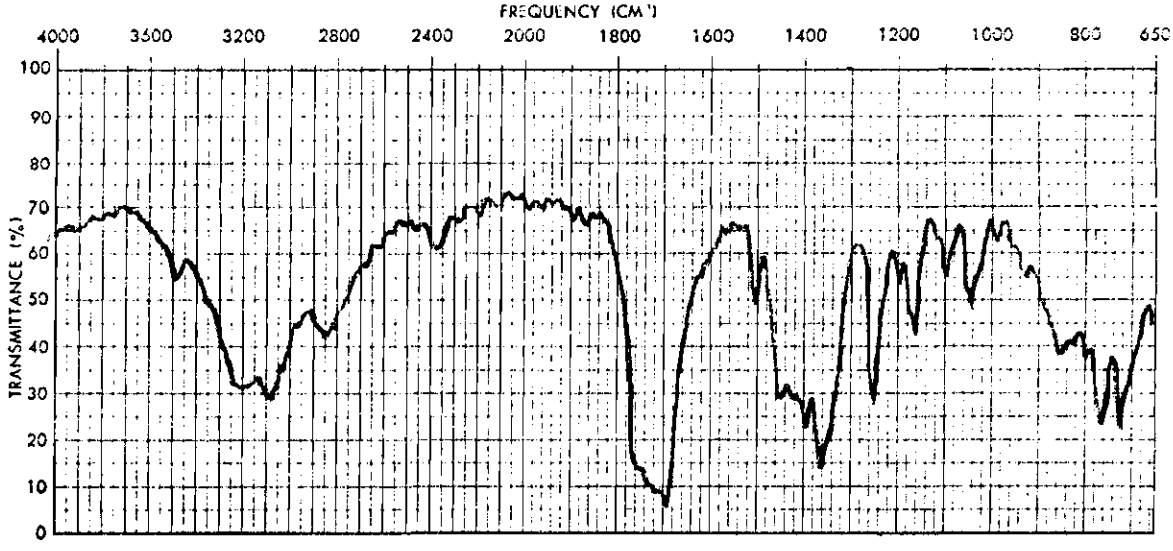


Figure 43. Infrared Spectrum of 5-Phenyl-5-[N-(benzylamino)]-barbituric Acid

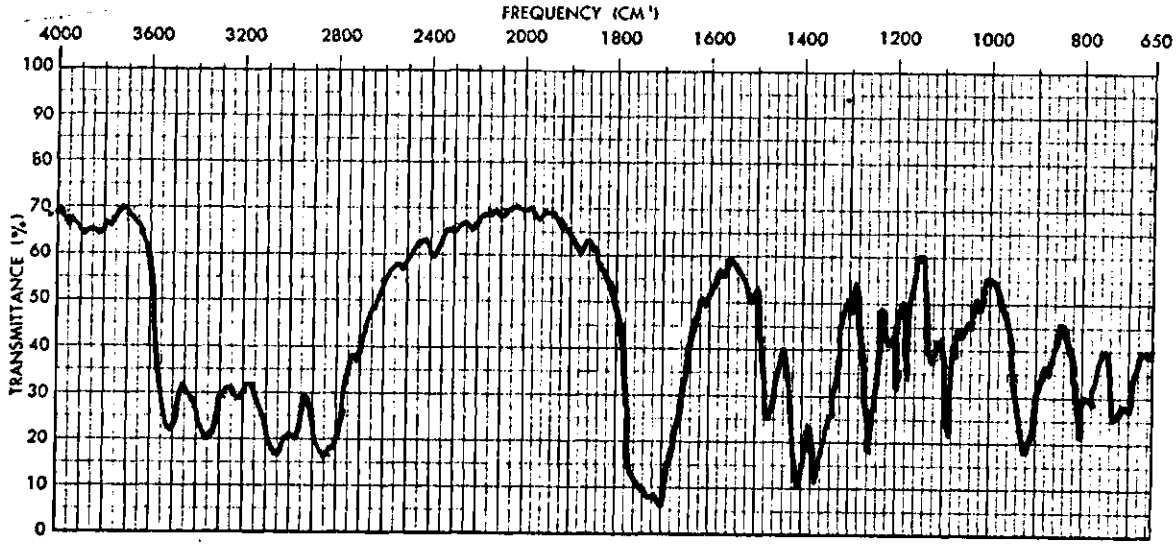


Figure 44. Infrared Spectrum of 5-Phenyl-5-[N-(3-amino-1-propanol)]-barbituric Acid

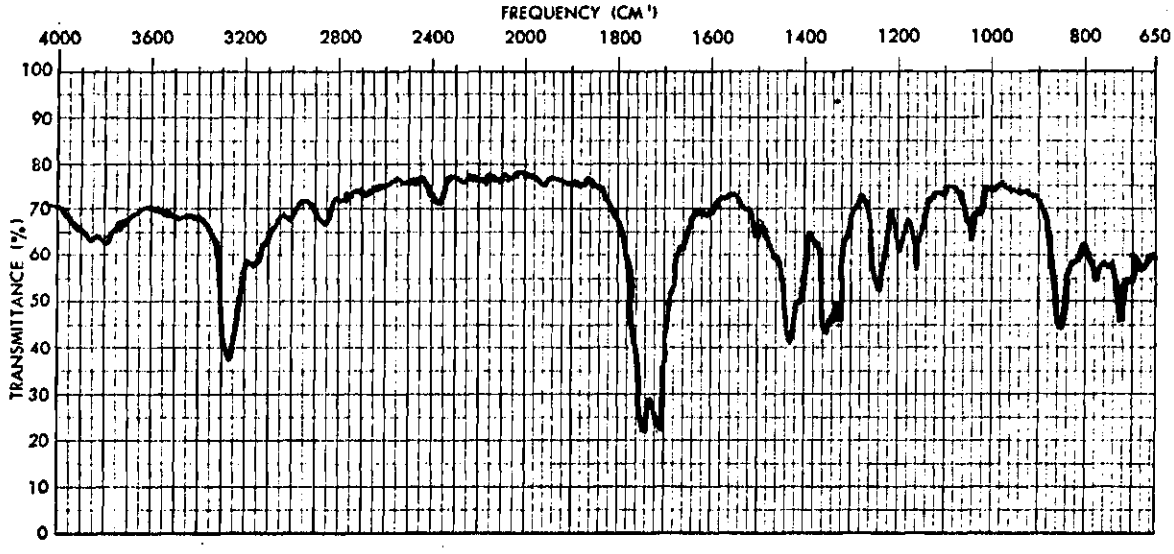


Figure 45. Infrared Spectrum of 5-Phenyl-5-[N-(l-amphetamino)]-barbituric Acid

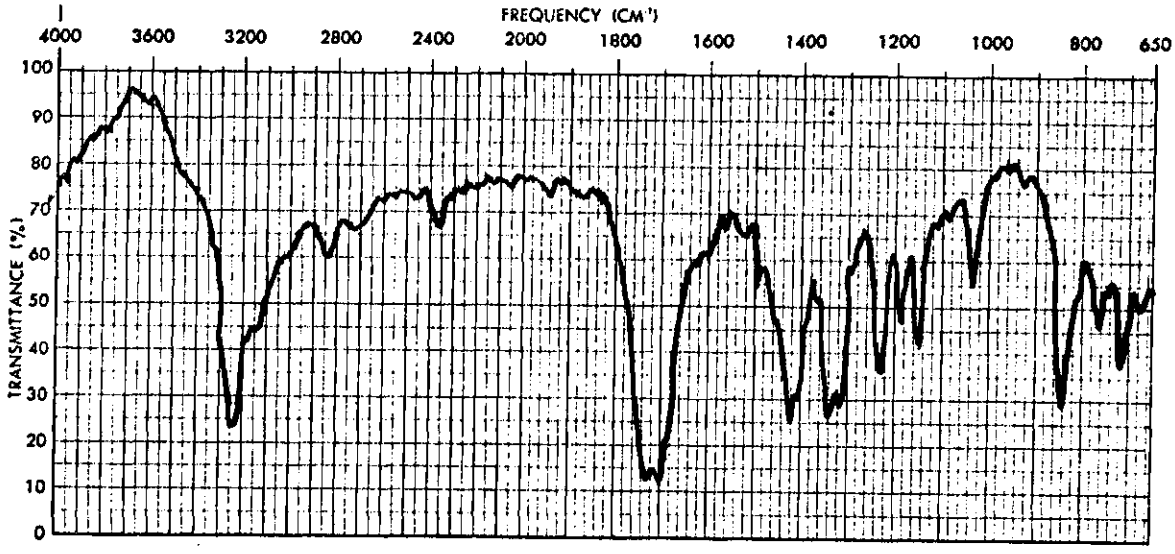


Figure 46. Infrared Spectrum of 5-Phenyl-5-[N-(d-amphetamino)]-barbituric Acid

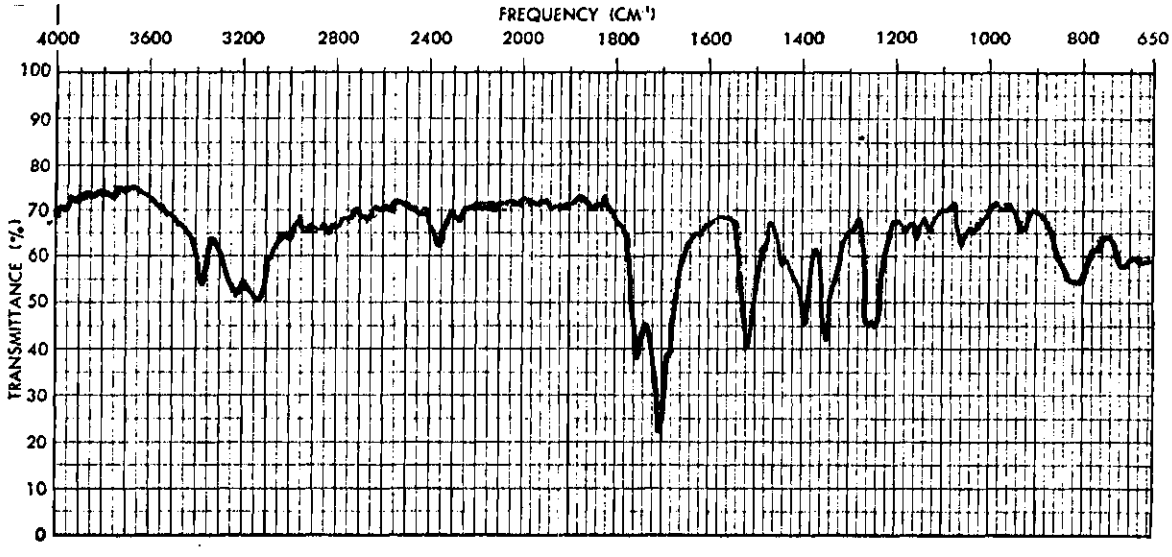


Figure 47. Infrared Spectrum of 5-Phenyl-5-[N-(p-phenetidino)]-barbituric Acid

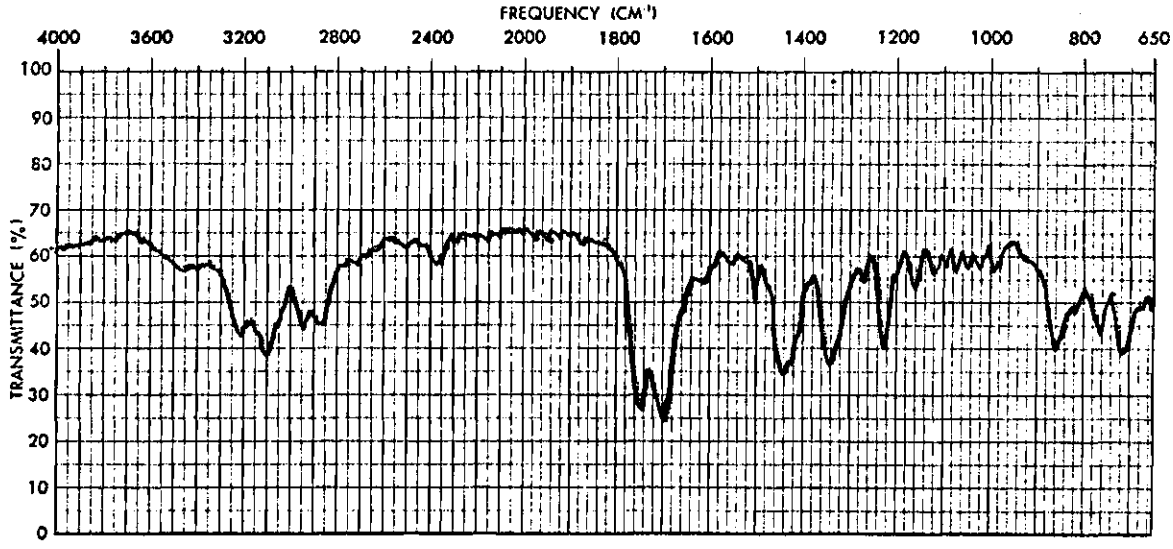


Figure 48. Infrared Spectrum of 5-Phenyl -5-[N-(4-benzylpiperidino)]-barbituric Acid

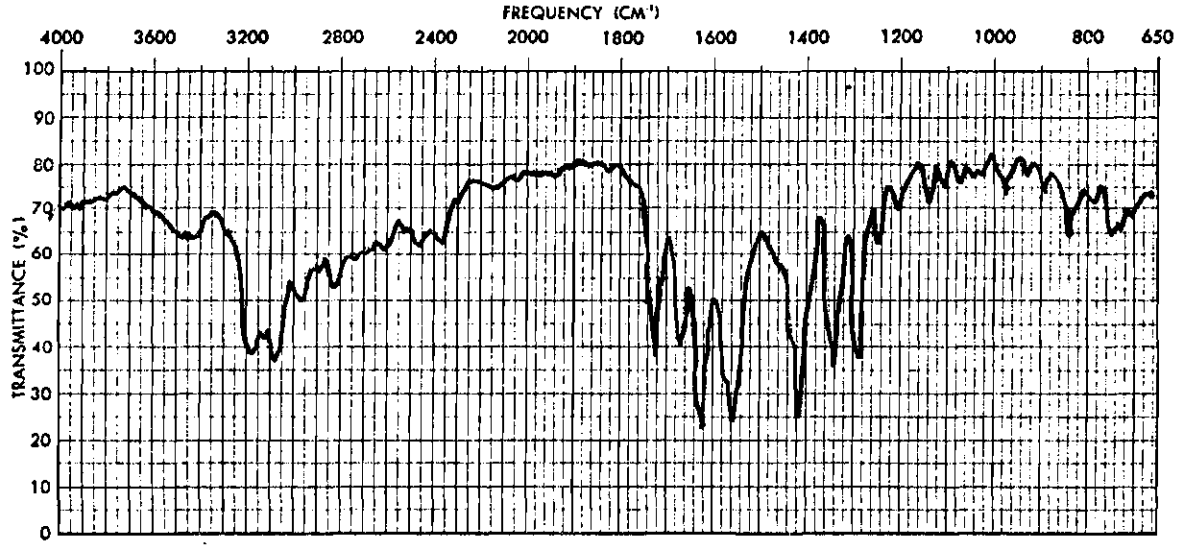


Figure 49. Infrared Spectrum of Salt of 5-Phenyl-[N-(2,2,6,6-tetramethylpiperidino)]-barbituric Acid

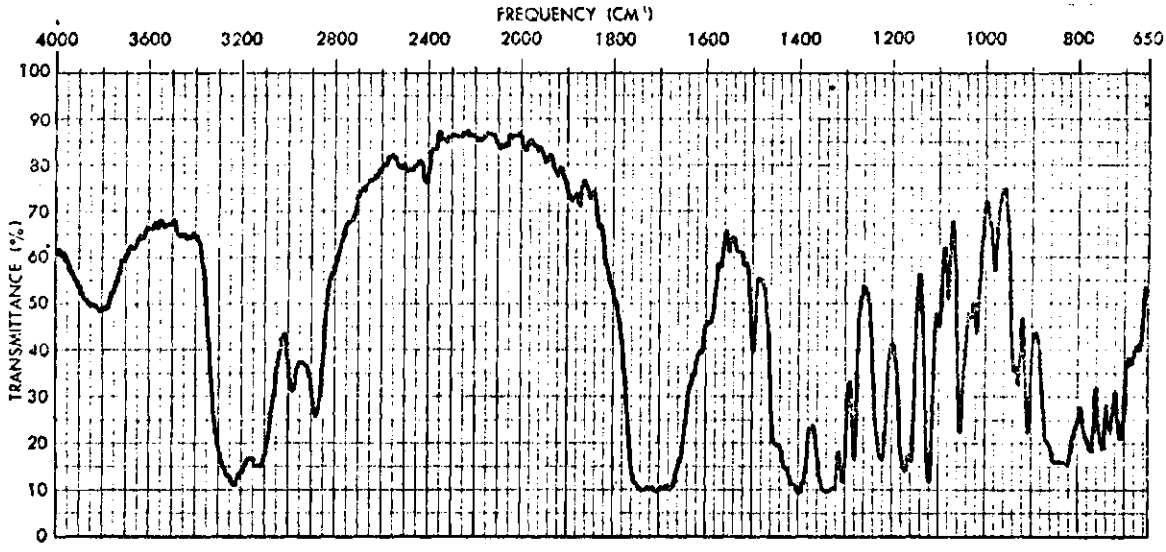


Figure 50. Infrared Spectrum of 5-Phenyl-5-[N-(morpholino)]-barbituric Acid

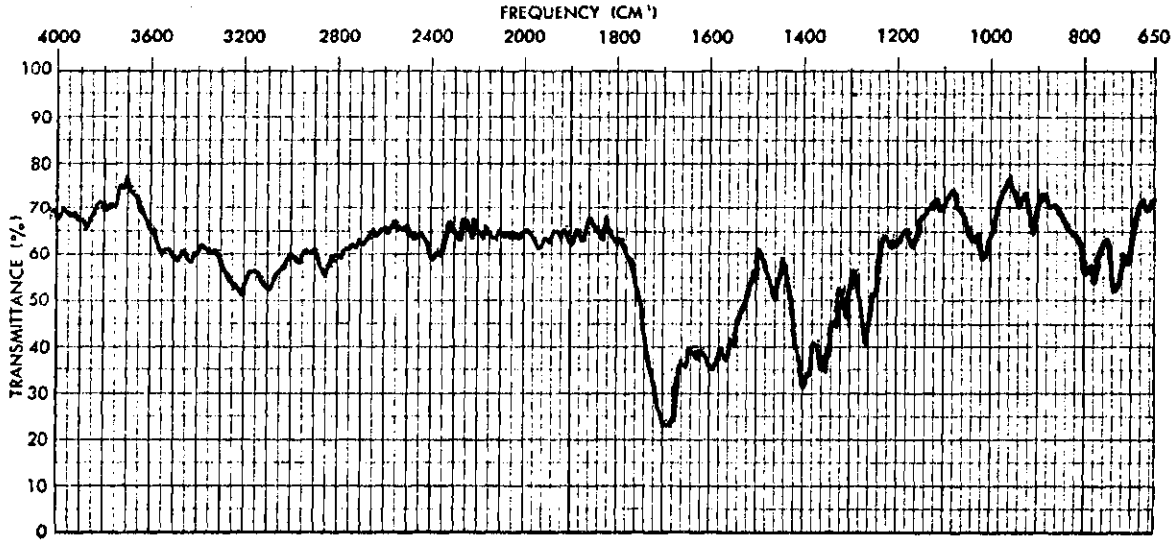


Figure 51. Infrared Spectrum of 5-Phenyl-5-[N-(N'-methylpiperazino)]-barbituric Acid

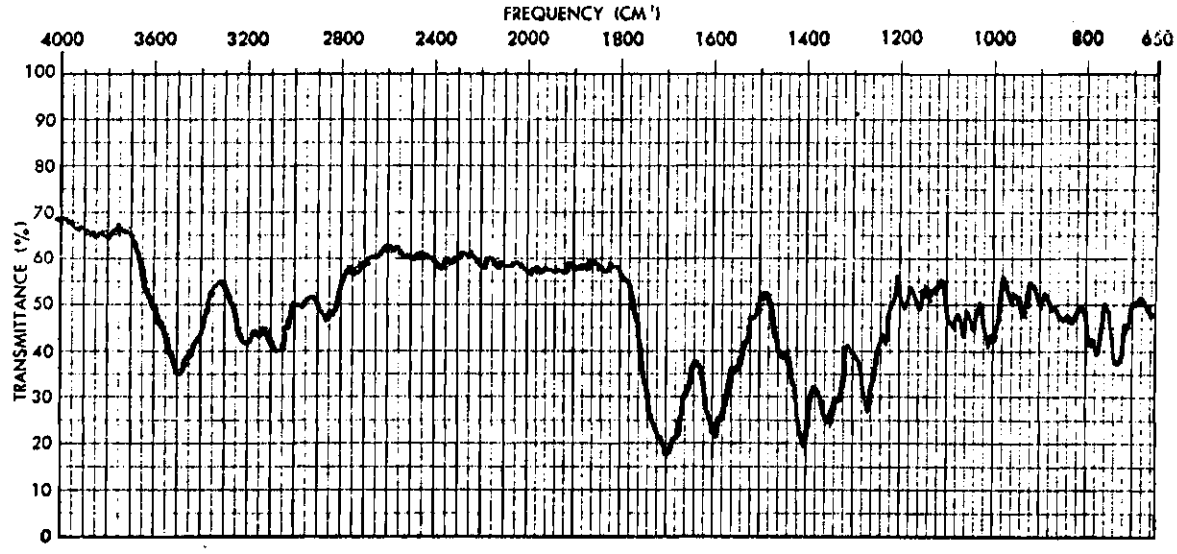


Figure 52. Infrared Spectrum of 5-Phenyl-5-[N-(N'-β-hydroxyethyl-piperazino)]-barbituric Acid

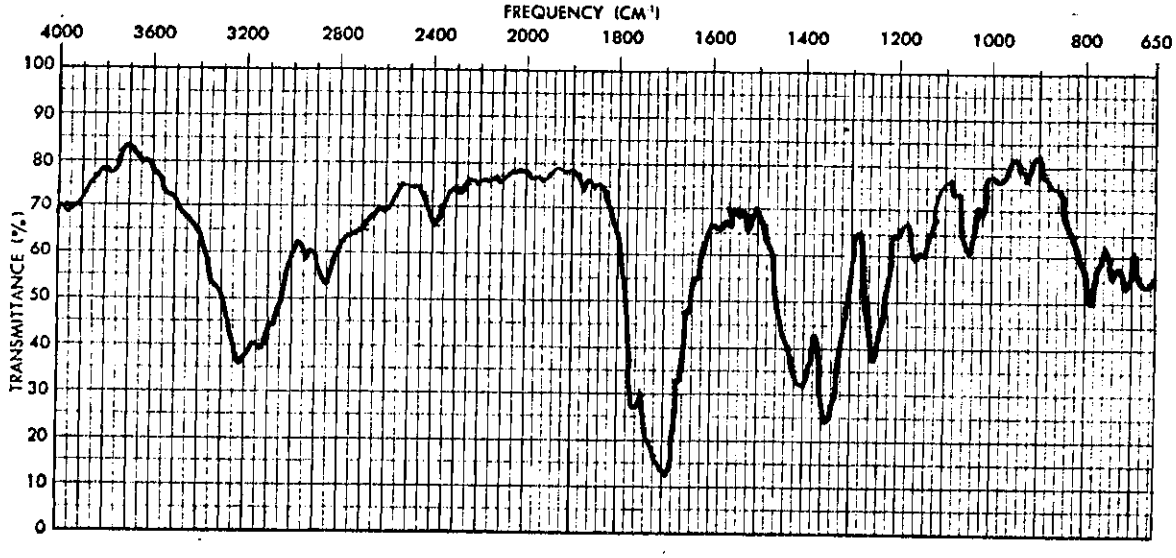


Figure 53. Infrared Spectrum of 5-Phenyl-5-[N-(1,2,3,6-tetrahydro-pyridino)]-barbituric Acid

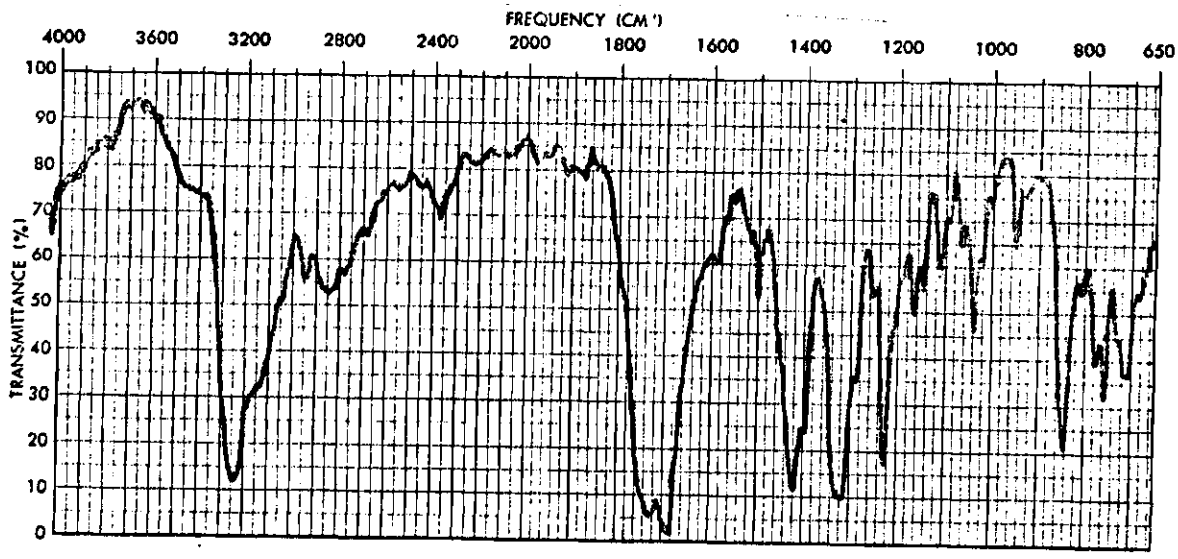


Figure 54. Infrared Spectrum of 5-Phenyl-5-[N-(1,2,3,4-tetrahydro-isoquinolino)]-barbituric Acid

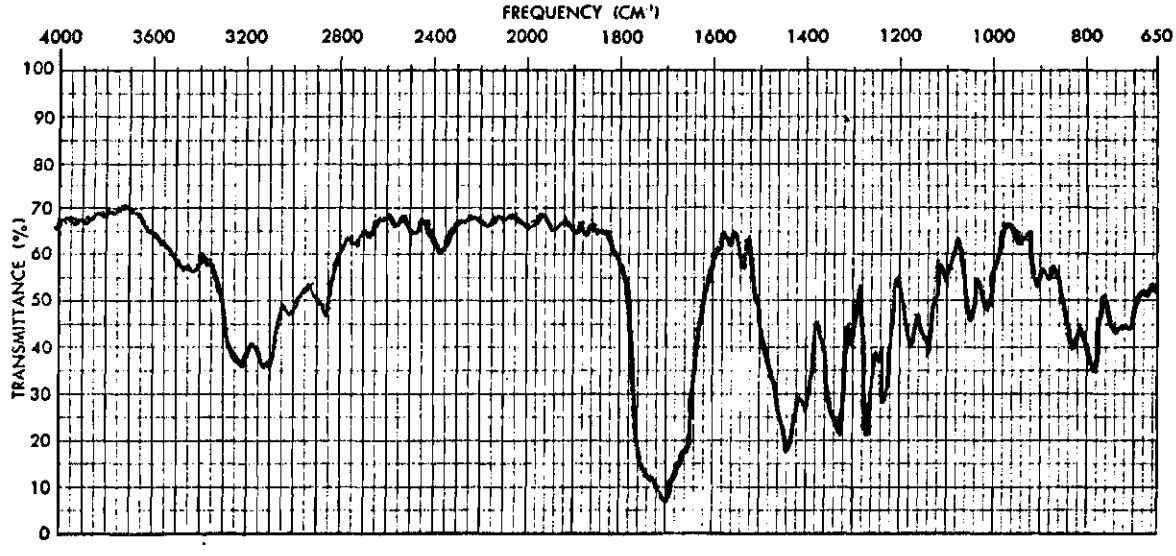


Figure 55. Infrared Spectrum of 5-Phenyl-5-[N-(ethyl-N'-piperazino-carboxylato)]-barbituric Acid

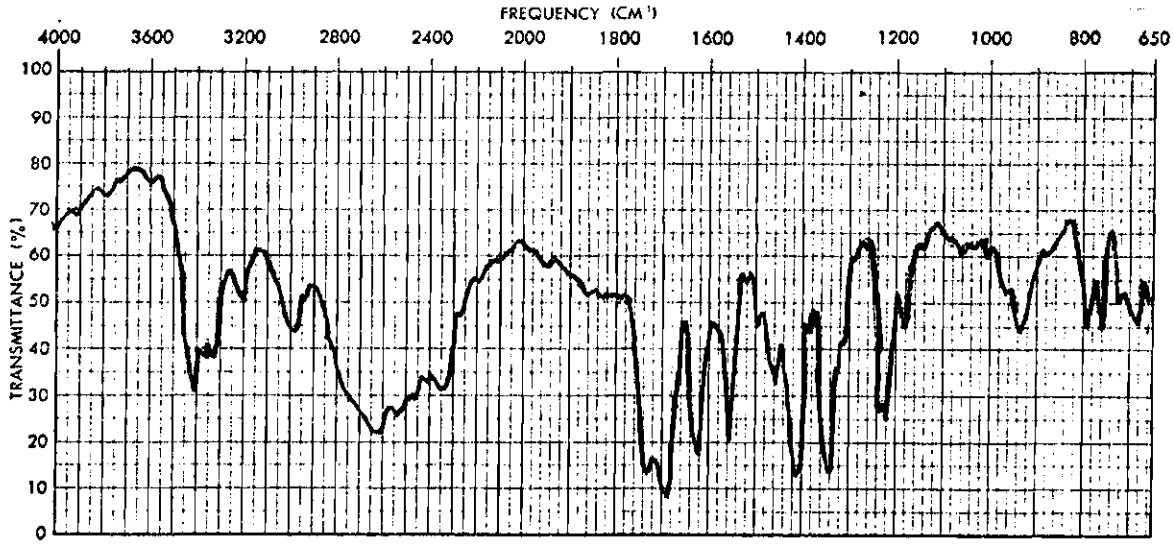


Figure 56. Infrared Spectrum of Salt of 5-Phenyl-5-[N-(2-aminopyrimidino)]-barbituric Acid

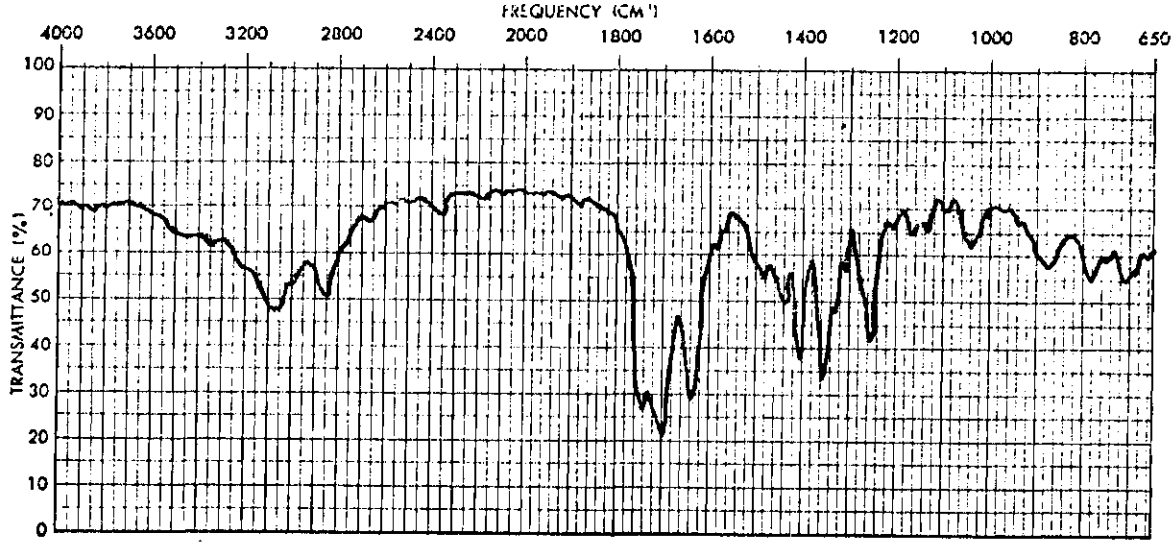


Figure 57. Infrared Spectrum of 5-Phenyl-5-[N-(N'-3(aminopropyl)-2-pyrrolidinono)]-barbituric Acid

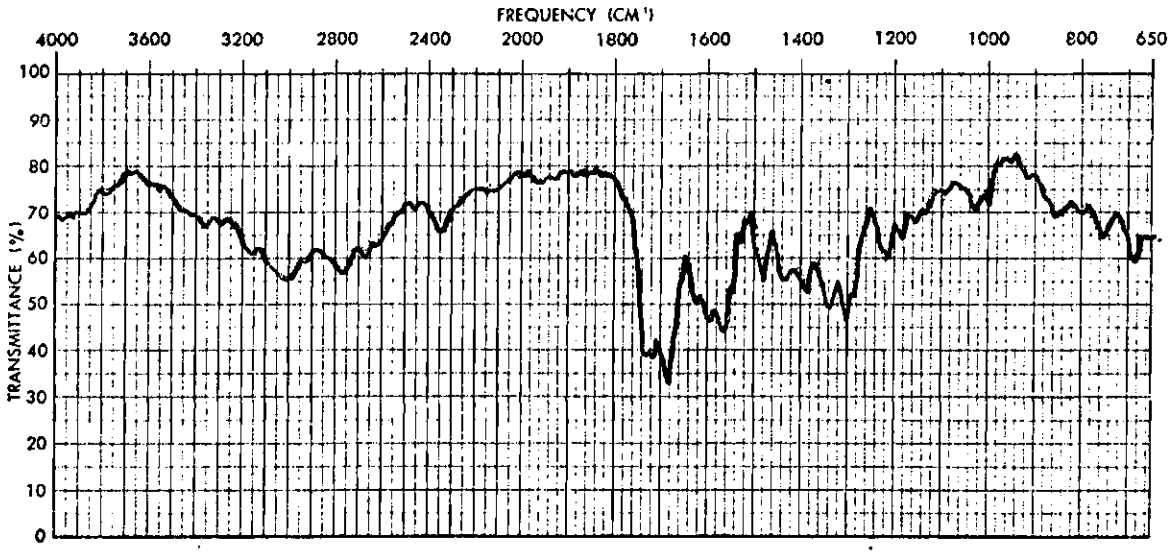


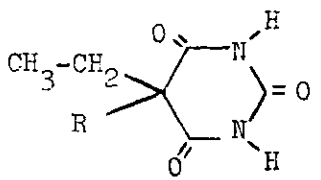
Figure 58. Infrared Spectrum of 5-Phenyl-5-[N-(4-aminoantipyreno)]-barbituric Acid

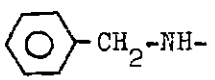
APPENDIX B

DERIVATIVES OF 5-ETHYLBARBITURIC ACID

Derivatives of 5-Ethylbarbituric Acid

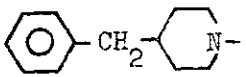
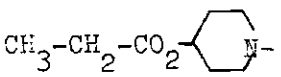
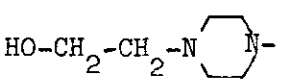
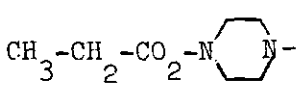
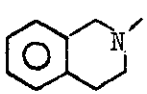
m/e (relative abundance)

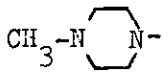




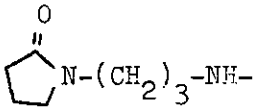
M.W.261 260(1) 232(2) 161(6) 156(7) 141(22)
128(7) 106(100) 98(8) 85(5) 56(43) 55(11)

M.W.199 241(11) 213(4) 212(56) 185(4) 184(61)
156(11) 141(36) 128(5) 98(11) 86(100) 85(16)
83(4) 56(41) 55(17)

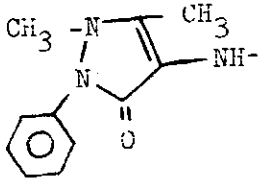
	M.W.329 329(10) 301(4) 300(19) 273(5) 272(24) 175(16) 174(100) 56(13) 55(13)
	M.W.311 282(6) 266(1) 254(9) 208(7) 157(9) 156(100) 83(4) 56(5) 55(6)
	M.W.284 254(6) 253(39) 98(14) 83(5) 59(100) 56(59) 55(26)
	M.W.312 312(9) 283(11) 267(6) 255(15) 210(7) 198(6) 158(11) 157(100) 156(21) 141(5) 128(10) 85(11) 83(8) 56(46) 55(24)
	M.W.287 286(5) 258(12) 230(8) 141(4) 133(23) 132(100)



M.W.254 255(8) 254(59) 128(4) 99(100) 98(12)
85(4) 83(6) 56(44) 55(18)



M.W.296 296(4) 267(9) 210(15) 198(28) 184(36)
183(10) 182(96) 156(10) 141(100) 128(26) 98(90)
85(13) 83(9) 56(67) 55(17)



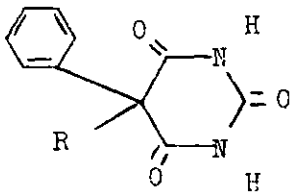
M.W.357 357(100) 328(21) 272(5) 271(28) 203(21)
202(57) 179(16) 128(12) 98(6) 85(7) 83(25)
56(38) 55(11)

APPENDIX C

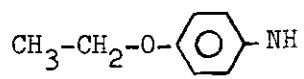
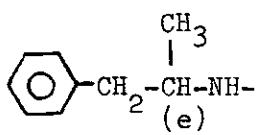
DERIVATIVES OF 5-PHENYLBARBITURIC ACID

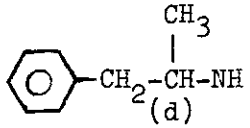
Derivatives of 5-Phenylbarbituric Acid

m/e (relative abundance)

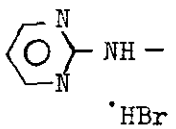


CH_3-CH_2-CH_2-NH-	M.W.261	261(11)	233(14)	232(100)	205(5)	204(44)
	132(10)	118(14)	117(6)	104(96)	103(5)	
 CH_2-NH-	M.W.309	252(4)	209(5)	204(6)	132(6)	118(6)
	117(4)	104(100)	103(8)			
CH_3-O-$(CH_2)_2$-NH-	M.W.277	233(14)	232(100)	204(8)	132(10)	118(6)
	117(5)	104(35)	103(8)			

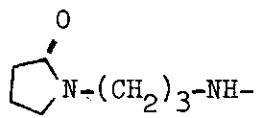
$CH_2=CH-CH_2-NH-$	M.W.259	218(5)	204(24)	132(20)	118(23)	117(19)
	104(100)	103(22)				
$HO-(CH_2)_3-NH-$	M.W.277	277(10)	234(5)	233(6)	232(40)	221(5)
	220(31)	214(6)	212(13)	205(13)	204(100)	132(10)
	118(24)	117(8)	104(54)	103(12)		
	M.W.339	340(12)	339(55)	297(10)	296(49)	292(6)
	274(13)	273(7)	225(11)	224(23)	204(18)	132(7)
	118(65)	108(100)	104(47)	103(7)		
	M.W.337	247(7)	246(52)	204(5)	203(3)	132(48)
	118(15)	117(24)	104(100)	103(30)		



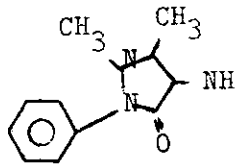
M.W.337 247(7) 246(52) 204(5) 203(3) 132(48)
118(15) 117(24) 104(100) 103(30)



M.W.378 205(4) 204(34) 203(100) 132(28) 118(70)
104(43) 103(11)

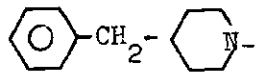
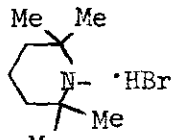
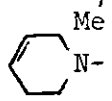
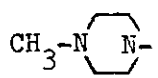
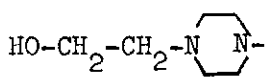


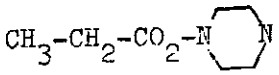
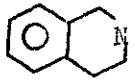
M.W.344 302(18) 301(100) 132(8) 118(12)
117(2) 104(5)



M.W.405 204(20) 119(14) 118(100) 104(6) 90(98)

M.W.289(5) 232(15) 205(6) 204(47) 174(20 132(18)
118(21) 117(80) 104(66) 103(25) 86(100)

	M.W.377	320(5)	204(7)	174(74)	132(10)	118(10)
	117(38)	104(53)	103(16)	91(100)		
	M.W.410	204(21)	126(100)	118(15)		
	M.W.285	204(22)	132(10)	118(26)	117(30)	104(58)
	103(17)	82(100)				
	M.W.302	303(4)	302(24)	204(10)	132(9)	118(16)
	117(39)	103(32)	99(100)			
	M.W.332	301(5)	204(37)	132(7)	118(100)	117(14)
	104(26)	103(8)				

	M.W.360	329(5)	328(19)	327(16)	326(7)	204(6)
	118(11)	117(6)	43(100)			
	M.W.335	218(11)	216(12)	215(12)	205(6)	204(57)
	132(52)	118(51)	117(28)	104(100)	103(32)	

APPENDIX D

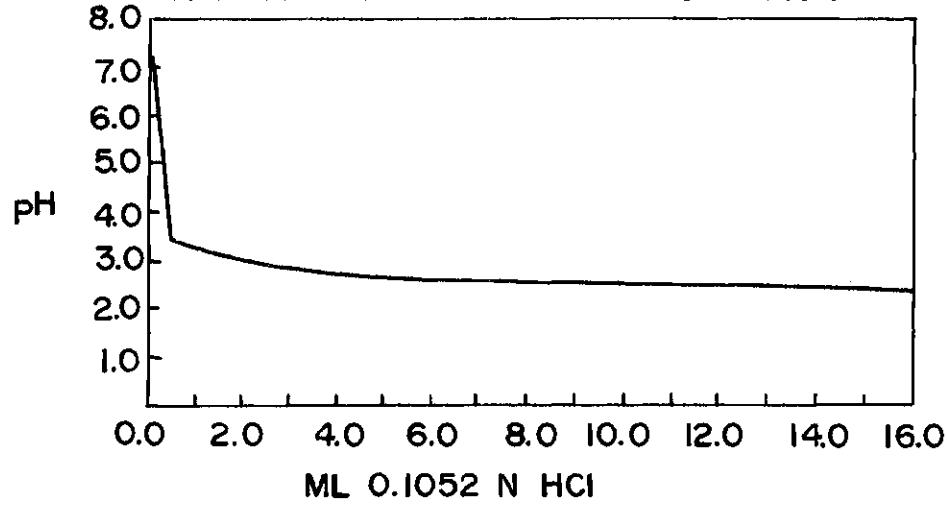
TITRATION DATA

One hundred milliliters of 95 per cent ethanol was titrated with 0.1052 N aqueous HCl. These results are reproduced graphically.

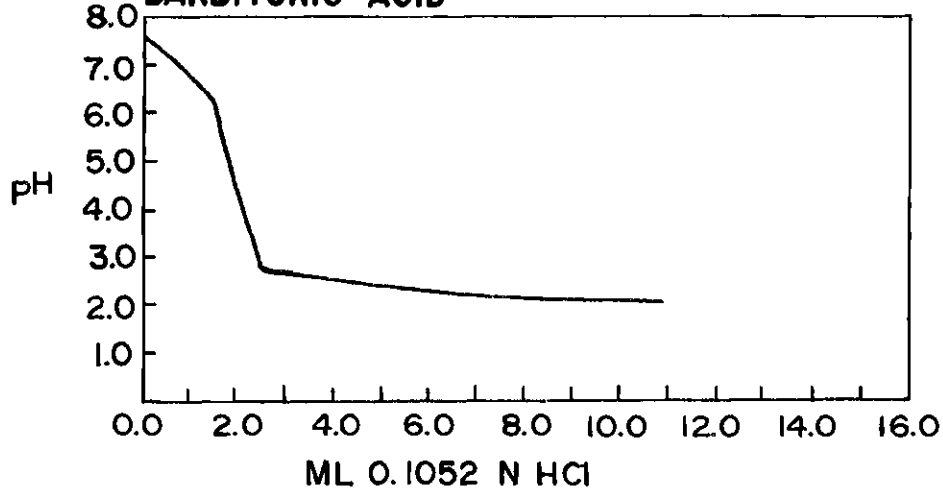
A solution of 0.0773 g (2.5×10^{-4} mole) of 5-phenyl-5-[N-(benzylamino)]-barbituric acid dissolved in 100 ml of 95 per cent ethanol was warmed to ca. 40° C. and titrated as rapidly as possible with 0.1052 N aqueous HCl while monitoring the reaction on a pH meter.

A solution prepared by dissolving 0.0653 g (2.5×10^{-4} mole) of 5-ethyl-5-[N-(benzylamino)]-barbituric acid in 100 ml of 95 per cent ethanol at 40° C. was titrated with 0.1052 N aqueous HCl while monitoring the reaction on a pH meter.

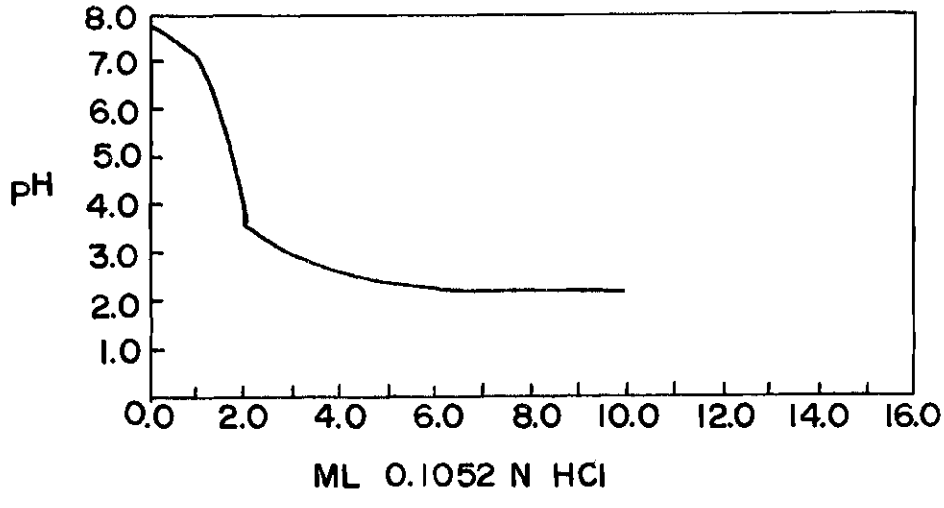
TITRATION OF 100ML OF 95% ETHANOL



TITRATION OF 5-PHENYL-5-[N-(BENZYLAMINO)]-BARBITURIC ACID



TITRATION OF 5-ETHYL-5-[N-(BENZYLAMINO)]-BARBITURIC ACID



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VITA

John J. Walker was born July 4, 1935 in Alma, Nebraska to Sylvia Seyler Walker and the late Thomas M. Walker. He attended public schools in Republican City, Alma, and Ragan, Nebraska and was graduated from the Ragan Consolidated Schools in 1952. After working two years with the Nebraska State Game Commission he entered the University of Nebraska in September, 1954 and received the Bachelor of Science degree in June, 1958. He then entered the United States Army for a period of two years, spending the major portion of this time in Bad Kreuznach, Germany. In June, 1960, he married the former Miss Charlene M. Carlson of Sumner, Nebraska and they are the parents of three children: Rachel, Nathan, and Samuel.

During the period 1960 to 1966, he taught in the Public Schools in Omaha and environs five years and spent one year at the Trinity Evangelical Divinity School in Chicago. At this time he also studied physics at Northwestern University in nearby Evanston. In September, 1966, he entered Atlanta University under a National Science Foundation grant to study for the Master's Degree in Chemistry and was awarded this degree in June, 1968. He entered the Georgia Institute of Technology that summer and received the Doctor of Philosophy in Chemistry degree in June, 1973. During a portion of this time at Georgia Tech, he held a part-time instructorship in the School of Chemistry.

He is presently employed as the Laboratory Director of Dettelbach Chemical Corporation in Atlanta, Georgia.